Behavioural and psychological characteristics and difficulties associated with Sotos syndrome in adolescence/adulthood: A follow-up study

by

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Declaration

I declare that the research reported in this thesis is an original piece of work, except otherwise stated by reference or acknowledgment. It has not been submitted for any other academic award and has been checked prior to submission.

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Thesis Abstract

Behavioural correlates of specific genetic conditions are increasingly researched. Such research is often of high priority for people with genetic conditions, their families and for healthcare professionals. This thesis sought to add to the knowledge base in relation to two genetic conditions.

Literature Review
The systematic literature review explores literature reporting on behavioural and psychological characteristics associated with Phelan-McDermid syndrome (PMS), a rare genetic condition caused by mutation at chromosome 22q13. Whilst previous summaries have indicated possible association with psychological and behavioural characteristics, there are no known systematic reviews to date. The prominent reported characteristics were developmental delay and delayed speech, while Autism Spectrum Disorder and autistic features were reported frequently. Evidence for other characteristics was less robust. Findings and conclusions are discussed in relation to quality appraisal, clinical implications and directions for future research.

Research Report
The research report comprises a seven-year follow-up study of temporal development in the behavioural and psychological characteristics associated with Sotos syndrome, a rare genetic condition associated with mutation in the NSD1 gene at chromosome location 5q35.2-q35.3. Parents and carers of individuals with Sotos syndrome who completed a previous study were invited to complete an online survey and telephone interview assessing adaptive behaviour, impulsivity, repetitive behaviour, challenging behaviour, mood, social communication and anxiety. The results indicated significant reductions in impulsivity and overactivity. There were indications of a changing picture of Autism Spectrum Disorder phenomenology over time. Aspects of repetitive behaviour continued to be prevalent, and an anxiety profile with peaks in panic, obsessive-compulsive behaviour and social avoidance was illustrated. Findings are discussed in relation to theoretical, clinical and research implications.

Critical Appraisal
The critical appraisal provides a reflection of the author's journey throughout the research process.

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First and foremost, I am truly grateful to all the participants and their families for taking part. I thoroughly enjoyed doing this research project with them and I was genuinely overwhelmed by how helpful participants and their families were in relation to data collection. This project couldn't have taken place without them and I hope that the results and feedback will be useful.

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[1] Research centre has not been named to maintain anonymity.

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LIST OF ABBREVIATIONS

Anxiety Depression and Mood Scale (ADAMS)

Attention Deficit Hyperactivity Disorder (ADHD)

Autism Diagnostic Interview-Revised (ADI-R)

Autism Diagnostic Observation Schedule (ADOS)

Autism Spectrum Disorder (ASD)

Challenging Behaviour Questionnaire (CBQ)

Childhood Autism Rating Scale (CARS)

Comparative genomic hybridization (CGH)

Cornelia de Lange syndrome (CdLS)

Developmental Delay (DD)

Diagnostic and Statistical Manual of Mental Disorders version-4 (DSM-IV)

Diagnostic and Statistical Manual of Mental Disorders version-5 (DSM-V)

Down syndrome (DS)

Fluorescent in situ hybridization (FISH)

Fragile X syndrome (FXS)

Hospital Anxiety and Depression Scale (HADS)

Intellectual Disability (ID)

Interquartile Range (IQR)

Mean (M)

Median (Med)

Mood Interest and Pleasure Questionnaire Short Version (MIPQ-S)

Nuclear receptor set-domain-containing protein (NSD1)

Number (N)

Online Mendelian Inheritance in Man (OMIM)

Phelan-Mcdermid syndrome (PMS)

Prader-Willi syndrome (PWS)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Repetitive Behaviour Questionnaire (RBQ)

Rubinstein-Taybi syndrome (RTS)

Sensory Experiences Questionnaire Short Form (SEQ)

Sociability Questionnaire for People with Intellectual Disability (SQID)

Social Communication Questionnaire (SCQ)

Spence Children's Anxiety Scale Parent Version (SCAS-P)

Standard Deviation (SD)

The Activity Questionnaire (TAQ)

Time 1 (T1)

Time 2 (T2)

Vineland Adaptive Behaviour Scale (VABS)

PART 1: LITERATURE REVIEW

A systematic review of the behavioural and psychological characteristics associated with Phelan-McDermid syndrome

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Target Journal: Molecular Autism

A systematic review of the behavioural and psychological characteristics associated with Phelan-McDermid syndrome

Lisa Humphries

1.1 Abstract

Background: Recent research has identified putative behavioural and psychological characteristics associated with Phelan-McDermid syndrome (PMS), a condition associated with genetic change in the 22q13 region. Understanding the behavioural phenotype associated with PMS is important to build awareness of the challenges faced by individuals and their families, and would enable services to be better equipped to offer appropriate support. Furthermore, insights into the behavioural/psychological correlates of genetic difference may aid scientific understanding of typical and atypical development.

Method: A systematic literature search on PsycINFO, Medline, Scopus and Embase was conducted in September 2017, to search for articles published since 1985 that reported on one or more behavioural and/or psychological characteristic associated with PMS. After study selection, 57 papers were identified and included for review. An adapted quality appraisal tool developed for use in reviewing research into characteristics of genetic syndromes was utilised.

Results: Varying degrees of developmental delay and intellectual disability with delayed speech were commonly reported as features associated with PMS. Autism Spectrum Disorder and autistic features were also reported frequently. Evidence of associations with other psychological characteristics was less robust. Study quality varied (quality score range 0.33-1.0), with participants recruited most commonly from regional and national support groups, use of a range of assessment measures and a high proportion of case studies.

Conclusions: Methodological limitations including the limited application of standardised assessments and lack of appropriate comparison groups make it difficult to generalise findings and make firm conclusions regarding the behavioural phenotype associated with PMS. More robust and in-depth strategies are required to explore characteristics to support elucidation of any associated behavioural phenotype. Nonetheless, this review has implications for services working with people with PMS and suggests individual assessment may be helpful following diagnosis to ensure tailored intervention can be made.

Keywords: behavioural phenotype, Phelan-McDermid syndrome, characteristics

1.2 Background

A significant number of children and adults in the UK are thought to have a diagnosis of a genetic syndrome with associated intellectual disability (ID), with estimates between 350,000 and 750,000 (Waite *et al.,* 2014). Many genetic syndromes are associated with a range of genetic and physical characteristics as well as behavioural and psychological features (Skuse & Slator, 2008). Specific patterns of behaviour are associated with individual genetic neurodevelopmental syndromes, to the degree that in some instances patterns of behaviour can indicate the presence of a syndrome (Harris, 2002).

Behavioural Phenotypes

The term 'behavioural phenotype' was introduced by Nyhan (1972) and a frequently adopted conceptualisation of the term has been defined by Dykens as "the heightened probability or likelihood that people with a given syndrome exhibit certain behavioural and developmental sequelae relative to those without the syndrome" (Dykens, 1995, p.523). Formal research into behavioural phenotypes burgeoned in the 1990s (Harris, 2002). Characteristics of a behavioural phenotype include social, linguistic, behavioural, cognitive and motor features (O'Brien, 2006). Waite *et al.* also highlight the importance of characteristics which are not directly observable, such as thoughts, emotions and motivational states and the way these are likely to interact with each other as well as physical characteristics. Research has indicated that while there are similarities between and within syndrome groups, there are also often variations and differences (Fidler *et al.*, 2008). Understanding an associated profile and the clinical implications as fully as possible for different syndromes may improve knowledge and understanding of services, as well as informing interventions and care planning (O'Brien, 2006) and increasing the possibility of early intervention. This may ultimately improve quality of life for individuals with genetic syndromes (Buckley, 2008). Some genetic syndromes, such as Down syndrome, Williams syndrome and Prader-Willi syndrome, have relatively well researched and described behavioural phenotypes, while understanding is typically at an earlier stage for more recently-described syndromes.

1.2.1 Phelan-McDermid Syndrome

Phelan-McDermid syndrome (PMS) is a rare genetic condition first identified in 1985 and 1988 (Phelan & McDermid, 2012). PMS can be referred to as 22q13 (or 22q13.3)

deletion syndrome, Telomeric 22q13 monosomy syndrome or PHMDS (McKusick, 2001).

Genetics

The syndrome is caused by a heterozygous contiguous deletion at chromosome 22q13, with the main gene thought to be affected being SHANK3 (located distally at 22q13.33). SHANK3 is a gene of interest in relation to neurodevelopmental and neuropsychiatric functioning independently of PMS, since it has been found to be mutated in a number of cases of ID, ASD (Leblond *et al.*, 2014) and schizophrenia (Gauthier *et al.*, 2010; de Sena Cortabitarte *et al.*, 2017). However, the genetic basis of PMS is complex, and understanding of this is evolving (e.g., Mitz *et al*., 2018). It is possible to be given a diagnosis of PMS without having a mutation affecting SHANK3, with some cases with interstitial deletions not affecting SHANK3 presenting with similar clinical characteristics to those with SHANK3 alterations (McKusick, 2001). The impact of variants of genes other than SHANK3 in the region is difficult to assess given the very high prevalence of SHANK3 in reported cases (Mitz *et al.*, 2018). Terminal deletions can extend from 22q13.2 to 22q13.33 and impact up to 108 protein-coding genes, with the average deletion size affecting nearly half of these genes (Mitz *et al.*, 2018). A number of other genes near SHANK3 are also highly expressed in brain tissue and represent genes in which variation is associated with diminished functioning.

The Phelan-McDermid Syndrome Foundation UK (2018) states that approximately 1500 individuals are diagnosed with PMS worldwide, although due to a high likelihood of undiagnosed cases the true prevalence is unknown.

Clinical and Physical Features

PMS is characterised by physical characteristics including dolichocephaly[2], large prominent ears, full brow, deep-set eyes, long eyelashes, full or puffy eyelids, droopy eyelids, a flat midface, full or puffy cheeks, a wide nasal bridge, a bulbous nose and a pointed chin (McKusick, 2001). Common features also include neonatal hypotonia and normal to accelerated growth (Phelan & McDermid, 2012). Suggested behavioural and psychological characteristics associated with PMS are developmental delay (DD), language difficulties, motor delay, autistic traits and increased tolerance to pain (Phelan & McDermid, 2012). Given that research findings have suggested autistic features may

[2] A condition where the head/skull is longer than would be expected.

be associated with PMS, and SHANK3 is also found to be mutated in a high proportion of people with Autism Spectrum Disorder (ASD), SHANK3 may ultimately represent an important clue as to possible mechanisms via which ASD can develop.

Autism Spectrum Phenomenology

ASD, a behaviourally-defined developmental condition, is diagnosed on the basis of distinctive behavioural patterns and observable impairments. ASD or ASD-like characteristics have been found in a large proportion of individuals with ID with estimates of between 31-35.4% (Brugha *et al.*, 2012) and have also been associated with many genetic conditions with differing manifestations and presentations. For example, ASD or ASD-like characteristics have been described in individuals with Cornelia de Lange syndrome and have been considered part of the behavioural phenotype of Fragile X syndrome (Moss & Howlin, 2009), although the profile of impairments and symptomatology may be syndrome-related. Moss *et al.* (2013) found that while 78.6% and 45.6% of individuals with Cornelia de Lange and 83.6% and 48% with Fragile X met cut-off criteria for ASD and Autism respectively, their scores on the Social Communication Questionnaire (Rutter *et al.*, 2003) were lower than an ASD group of individuals. They also found that individuals with Cornelia de Lange showed greater impairments in communication whereas individuals with Fragile X showed higher levels of repetitive behaviour, illustrating the potentially varying profile of characteristics and phenomenology leading to individuals meeting diagnostic criteria. The study of different Autism Spectrum phenotypes and their associations with genetic factors has the potential to elucidate the nature of ASD, and its possible underpinnings.

1.2.2 Previous Reviews

A number of papers have offered a summary or general review of the literature on PMS, although to the author's knowledge none represent systematic searches of the literature nor have they offered a focus on behavioural and psychological characteristics. Summaries of the most common presentations of PMS have listed, alongside physical characteristics such as dysmorphic features, global DD, absent or delayed speech, hypotonia, and ASD (Costales & Kolevzon, 2015; Phelan & McDermid, 2012). This is consistent with older summary papers such as Havens *et al.* (2004) and Cusmano-ozag *et al.* (2007). Havens *et al.* reported 96% of cases in published research exhibited global DD, 96% absent speech and 86% increased tolerance to pain. Cusmano-ozag *et*

al. reviewed 107 cases in the literature and concluded that 98% displayed DD, 96% absent and delayed speech, 86% hypotonia and 44% autistic behaviours.

Mitz *et al.* (2018) recently published a review of the prevalence of gene loss and predicted loss pathogenicity for a set of selected genes other than SHANK3 potentially affected by genetic variation on terminal 22q and with putative contribution to PMS. Using computational (as opposed to directly clinical) methods, they found that groups of protein-coding genes related to a number of relevant processes, such as brain development and organisation as well as subsequent synaptic function and circadian rhythm, and may play a part in atypical neurofunctional development in PMS. They highlight the need for further clinical study of these possibilities.

1.2.3 Rationale and Objectives of Review

The behavioural phenotype of PMS has not been well defined and there are no known systematic reviews. PMS can have a huge impact on an individual and their family. A more thorough understanding and awareness of associated characteristics would begin to inform services and interventions to tailor appropriately to individual needs. Understanding of this syndrome may also ultimately contribute to the elucidation of genetic and neurobiological processes associated with typical and atypical development, and diagnoses such as ASD. This systematic review sought to identify, synthesise and critically appraise the literature available on the behavioural and psychological characteristics associated with PMS.

1.3 Method

The method and results have been informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance (PRISMA; Moher *et al.*, 2009).

1.3.1 Search Strategy

A scoping search carried out on the Google search engine and the Online Mendelian Inheritance in Man website (OMIM; McKusick, 2001), established alternative titles for PMS and its associated gene location. To capture the different variations, the gene loci were also used in the search strategy. Checks were made during initial scoping to ensure the list of search terms used detected the same number of papers as a more

extensive list of individual variations. The list of behavioural/psychological terms was developed through consultation with systematic reviews in the behavioural phenotypes literature, examination of the OMIM website (for PMS and other genetic conditions) and consultation with a research lecturer specialising in the field from a research centre for neurodevelopmental disorders[3]. Behavioural and psychological terms were defined as social, linguistic, behavioural, psychological, emotional, cognitive and motor features (O'Brien, 2006; Waite *et al.*, 2014). It was acknowledged that the definition of these terms may be variable, although every effort was made to ensure replicability.

Searches were conducted by combining terms for PMS with behavioural and psychological search terms. Four databases were utilised: Ovid PsycINFO (1872-present), Ovid Medline (1946-present), Ovid Scopus (1996-present) and Ovid Embase (1980-present). These databases were used to ensure that a wide range of material could be explored. Different search fields were utilised on each database, this variation was due to the databases' unique search engines and was supported by consultation from library services. All searches were conducted on 6th September 2017. Table 1 displays the search terms and the initial electronic database search. A total of 1359 papers were returned by the initial searches.

[3] Research centre not named to maintain anonymity.

Table 1. Initial database search

Database **(search fields)**	**PsycINFO** ('All fields')	**Medline** ('title, abstract, keyword')	**Scopus** ('title, abstract, keyword')	**Embase** ('title, abstract')
Search Terms	phelan mcdermid OR phelan-mcdermid OR phelan mcdermid syndrome OR phelan-mcdermid syndrome OR 22q13 OR 22q13.3 AND behavio* OR psych* OR clinical OR emotion* OR cognit* OR mental OR phenotyp* OR abilit* OR intellectual disabilit* OR learning disabilit* OR intelligen* OR IQ OR developmental abilit* OR developmental delay OR retardation OR intellect* OR processing OR development* OR language OR linguistic OR communicat* OR speech OR verbal OR motor OR psychomotor OR autis* OR autis* spectrum OR ASD OR repetiti* OR ritual* OR stereotyp* OR social OR sociability OR anxi* OR mood OR depressi* OR affect* OR bipolar OR attention* OR sensory OR sleep OR memory OR executive function* OR function* OR adaptive behavio* OR maladaptive OR overactivit* OR aggress* OR hyper* OR phobia OR ADHD OR attention deficit hyperactivity disorder OR impulsiv* OR self-injur* OR temper OR personalit* OR problem solving OR obsess* OR compulsi*			
Total per database	82	309	598	370
Total combined	1359			

1.3.2 Selection Strategy

A systematic filtering process with clear inclusion and exclusion criteria was used to assess relevance and suitability of the articles. A flow chart of the search and selection strategy is detailed in Figure 1 and outlines the number of papers included and excluded at each stage. Electronic database filtering utilised the criteria outlined in Table 2, leaving 1273 papers. Publication year was limited to 1985 to present, as the first cases of PMS were reported in 1985 and 1988 (Phelan & McDermid, 2012). Searches included research conducted worldwide, although shortlisted papers were limited to the English language.

Table 2. Inclusion and exclusion criteria used during the database search

Inclusion Criteria	**Exclusion Criteria**
Published between 1985 to present day	Published before 1985
Peer reviewed	Not peer reviewed
Journal article with primary research	Conference proceeding, magazine, dissertation, book
Paper written or published in English	Papers published in any other language than English

A manual filtering process was employed to further screen the titles and abstracts. Additional inclusion and exclusion criteria were added at this stage to those in Table 2 and are detailed in Table 3.

Table 3. Inclusion and exclusion criteria used during screening stage

Inclusion Criteria	**Exclusion Criteria**
Papers reporting directly on PMS	Papers with no direct relevance/focus on PMS
Papers reporting on human participants	Papers reporting on animal participants only
Papers reporting on psychological/ behavioural feature/characteristic	Papers reporting on physical health or genetic aspects only
Papers reporting on one or more psychological/ behavioural characteristic in title, abstract or keywords specifically in relation to a case(s) described or reported	Papers referring to one or more psychological/ behavioural feature/characteristic in the background information in the abstract but do not suggest that data are reported specifically related to one or more participants with PMS. Erratum or article replies

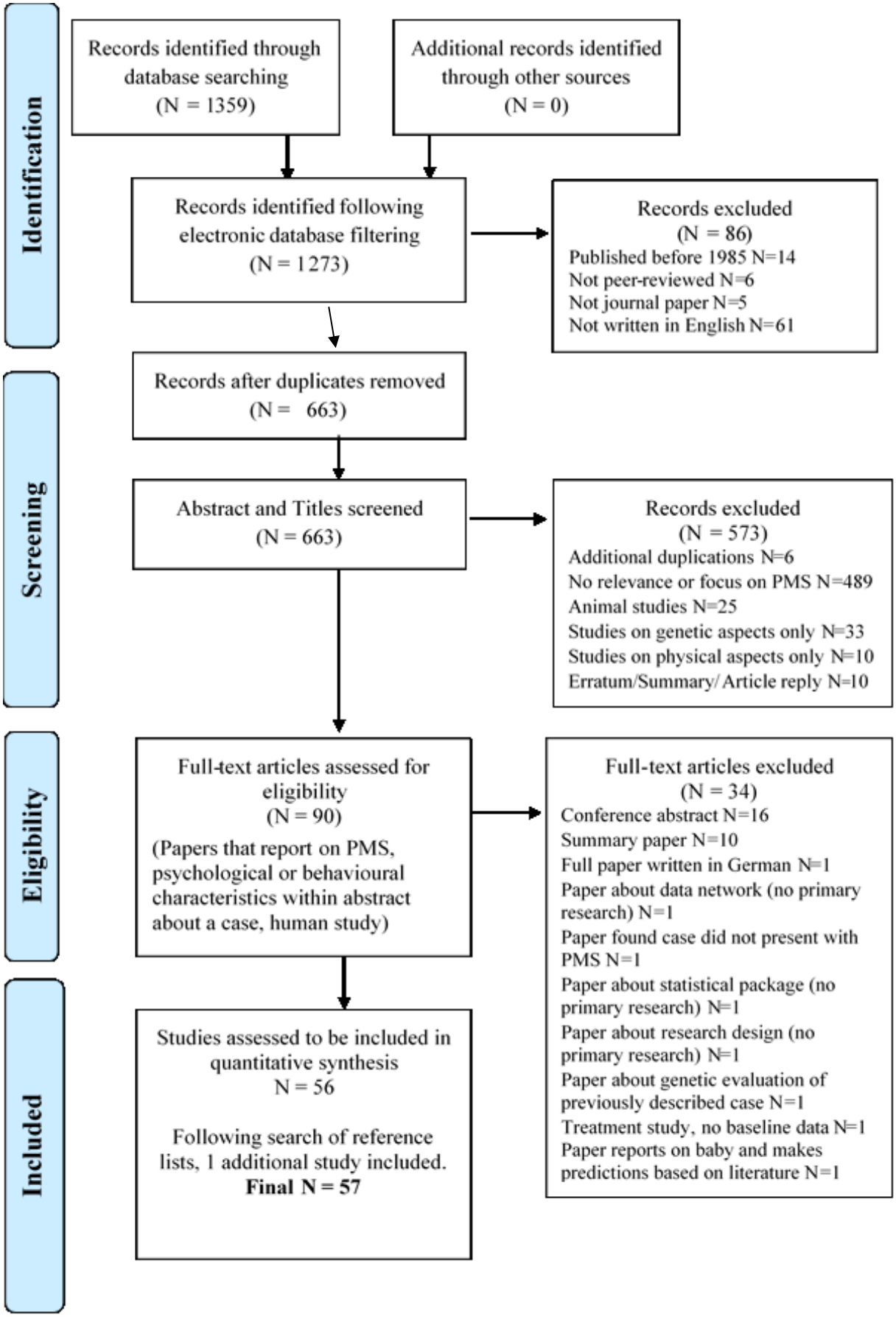

Figure 1: PRISMA flow chart illustrating search strategy and filtering process

Ninety papers were considered appropriate to read in full to assess eligibility. The same inclusion and exclusion criteria outlined in Tables 2 and 3 were utilised during this stage. Following this, 56 papers were considered eligible. The reference lists of these papers were also checked, and an additional paper was identified which had not shown up on the database search, resulting in the final number of papers being 57. Papers were divided into two categories: those with case study methodologies and those with cohort methodologies. A case study methodology was defined as studies that described a case or a series of cases individually (papers in this category had six or fewer participants). Detailed analysis of case studies is beyond the scope of the current review, although data are included in Appendix A and summarised in succeeding sections. A cohort methodology was defined as studies that described a group of cases at a collective level.

1.3.3 Data Extraction Process

Data extraction was carried out systematically using a data extraction guide developed by the author to maintain a systematic approach specific to the topic (see Appendix B). Extraction was completed with support from an undergraduate student on placement with the affiliated research centre.

1.3.4 Quality Appraisal

To assess quality of the cohort papers, each was rated using an adapted version of the quality criteria developed by Richards *et al.* (2015) which assessed sample identification, confirmation of syndrome and assessments utilised. This quality appraisal tool provides a recognised measure for assessing quality of papers in the field of genetic syndromes. Criteria were originally developed for assessing prevalence of ASD in genetic syndromes therefore small adaptations were made to focus the criteria on the behaviours of interest in the present review. The final criterion of 'assessment' was adapted to incorporate assessments of a range of characteristics. Appendix C displays the quality criteria along with the visual colour coding. Following Richards *et al.*, an overall quality rating score, with possible values between 0 and 1, was calculated by dividing the study's total score by nine (the total possible score).

1.3.5 Meta-analysis

Because fifteen papers were available in which it was reported how many participants met criteria (by some definition) for ASD, pooled prevalence estimates were generated for this characteristic using MetaXL 2.0 (Barendregt & Doi, 2011). A random effects model was selected due to its assumption of variability from both sampling error and differences at the level of the nature of the studies (Barendregt & Doi, 2011). An additional quality effects model was generated, which also adjusts weightings according to the quality ratings assigned during quality appraisal.

This was not carried out for other characteristics, due to low numbers of papers and/or lack of consistency between papers in how characteristics were reported, defined or measured.

1.4 Results

1.4.1 Case Studies

Thirty-three papers were identified that utilised a case study methodology and offered case descriptions. This indicated that a significant proportion of available data on the behavioural and psychological characteristics of PMS is based on small samples. These papers reported on six or fewer participants, with a total of fifty-seven cases[4], aged between 4 months and 70 years[5]. Participants were sometimes recruited from genetics departments (24% of papers) and ongoing research studies (3% of papers), although a high proportion of studies did not provide recruitment details (73% of papers). The characteristics outlined in these papers are detailed in Appendix A. The most commonly reported characteristics in cases included delayed speech development (91%), DD or ID (89%) and delayed motor development (81%). It was noted that the extent or level of DD or ID was rarely detailed or defined. Papers also reported cases with autistic features (42%) and behavioural problems (35%). Autistic features included poor eye contact (N=8), stereotypic movements (N=7), poor social interaction (N=4) and restricted interests (N=3). Three papers reported three cases where ASD had

[4] The author is not aware of any cases reported more than once in the case study papers.
[5] Based on available information.

been diagnosed using criteria in the Diagnostic and Statistical Manual of Mental Disorders Version four (DSM-IV; Goizet *et al.*, 2000; Macedoni-Luksic *et al.*, 2013; Prasad *et al.*, 2000) while one paper directly stated that a case did not meet diagnostic criteria (Gorker *et al.*, 2016). Behavioural problems were often described as aggression (N=10) and restlessness (N=5). Self-aggressive or injurious behaviour was also noted in five cases (Goizet *et al.*, 2000; Schmidt *et al.*, 2009; Webster & Raymond, 2004). In addition, a proportion of papers were found to report cases with sleep difficulties (19%), high pain threshold (16%), attention and hyperactivity (14%), anxiety (11%), bipolar disorder (9%), depression (7%) and schizophrenia (2%).

Generally, these papers tended to offer case descriptions based on clinical judgements, observations and verbal reports from parents. Use of standardised assessment measures was limited (only 14 papers). When studies utilised assessment measures, this was a combination of screening instruments with parents, for example the Vineland Screener (van Duijn *et al.,* 2009) in three papers, and some direct assessment with participants, the most common of which was the Bayley Developmental Test (Bayley, 2005) in three papers.

1.4.2 Cohort Studies

Twenty-four papers utilised a cohort methodology and all reported on seven or more participants, with an age range of 5 months to 64 years 2 months[6]. The details of these papers are presented in Appendix D. Participants were recruited from a range of sources including national foundations of support (38% of papers), genetic departments (25% of papers), ongoing research studies (16% of papers) and regional parent support groups (8% of papers) while a small proportion did not provide recruitment details (13% of papers). In total 993[7] participants were reported on, while Phelan *et al.* (2001) acknowledged that their recruitment strategy had included participants reported in two other studies identified in the current search, one of which was a case study (Doheny *et al.*, 1997) and the second a cohort study (Nesslinger *et al.*, 1994), and Reierson *et al.* (2017) also stated 'some' of their participants had participated in the study by Soorya *et al*. (2013). The level of genetic information provided within papers was found to be detailed, often providing karyotype followed by molecular analyses. There were rare

[6] Based on available information.

[7] Total figure does not take account of repeats due to number of repetitions being unclear, as indicated in the text.

(two papers) instances when papers stated a diagnosis of PMS without providing confirmation of syndrome. Only three papers (12.5%) obtained the highest quality rating for sample identification, while 20 (83.3%) obtained the highest quality rating for syndrome confirmation. All studies reported on a variety of behavioural and psychological characteristics, with a range of measures/instruments utilised. The most commonly reported characteristics were DD/ID in 20 papers, delayed speech and language abilities in 18 papers, ASD and autistic features in 15 papers. Behavioural features and motor skills were also reported frequently, in 10 and 9 papers respectively. A smaller proportion of studies were found to report on sleep (four), sensory experiences (four), mental health (four), attention and hyperactivity (three) and high pain threshold (three). Findings have been grouped into categories according to characteristic and displayed in Tables 4 to 13. In addition, studies/papers that scored six or more out of nine (a rating of 0.67 or above) on the quality rating tool have been further highlighted within the text to indicate key papers in this review (following Mulder *et al.*, 2016).

Developmental Level

Twenty papers reported on developmental level. The results are displayed in Table 4. Findings suggest that DD and ID were commonly found within participants with PMS. DD refers to a delay in reaching developmental milestones and ID refers to cognitive delay and functional/adaptive impairment. These terms are often used together when referring to developmental level. Descriptions varied, with half of the papers appearing to discuss global DD/ID quite generally (N=10) and half mentioning categories such as 'mild', 'moderate', 'severe' and 'profound' levels of functioning (N=10). It was difficult to categorise participants specifically, due to the tendency for papers to group participants into broader categories (e.g., Egger *et al.* (2016) reported 7/7 participants showed *mild to moderate and moderate to severe* ID). Seven studies did not specify how developmental level had been measured or relied on parental report, while seven studies used direct in-person assessments and four relied on versions of the Vineland Adaptive Behaviour Scales (Sparrow *et al.,* 2005; van Duijn *et al.,* 2009), which assesses adaptive behaviour on the basis of parent/caregiver report. This posed some difficulty in directly comparing/amalgamating results. The Wechsler Intelligence

assessments (Wechsler, 1991) were used only with two participants on two occasions (Philippe *et al.*, 2008; Zwanenburg *et al.*, 2016).

The number of participants reported in each paper varied from 7-71. Sarasua *et al.* (2011) reported on the largest sample, while they relied on parental report to describe developmental level and utilised no direct assessment with participants. Glaser and Shaw (2011) reported that compared with an Autism group, participants with PMS were more impaired, although study quality was rated as low. The overall quality of the papers was variable (ranging from 0.33-0.89), and ten were identified to have good quality ratings (Denayer *et al.,* 2012; Dhar *et al.*, 2010; Egger *et al.*, 2016; Kolevzon *et al.*, 2014; Manning *et al.*, 2004; Phelan *et al.*, 2001; Shaw *et al.*, 2011; Soorya *et al.*, 2013; Wang *et al.*, 2016; Zwanenburg *et al.*, 2016). In this selection of papers, PMS was always confirmed genetically using molecular analyses, yet they had varying methods of sample identification and characteristic measurement. DD or ID was described for all participants in this selection. Severity of delay was also found to be positively associated with deletion size in four papers (Luciani *et al.*, 2003; Sarasua *et al.*, 2011; Wilson *et al.*, 2003; Zwanenburg *et al.*, 2016).

Table 4. Summary of studies reporting on developmental level in PMS

Reference	Quality Criteria: Sample	Quality Criteria: Syndrome	Quality Criteria: Characteristic	N	Assessment/measure	Findings	Quality Rating
Denayer *et al.* (2012)				7	Parental report Observation Dutch version of Vineland Adaptive Behaviour Scale for Individuals with ID	57% severe ID 43% profound ID 100% developmental delay and poor adaptive behaviour 86% showed poor communication 71% socialisation deficits 71% had developed some skills of daily living.	0.78
Dhar *et al.* (2010)				13	Not specified/reported	100% developmental delay.	0.67
Egger *et al.* (2016)				7	Snijders-oomen Nonverbal Intelligence Test Vineland Screener	100% mild and moderate to severe ID Developmental functioning ranged from 1.0 to 6.3years.	0.67
Glaser & Shaw (2011)				18	Developmental Profile-III	Mean mental age of 1.91 years for the group Adaptive and cognitive domains severely compromised.	0.44
Kolevzon *et al.* (2014)				9	Mullen Scales for Early Learning Leiter International Performance Scale-R Vineland Adaptive Behavior Scales-II	100% ID and poor adaptive functioning Mental age equivalent ranged from 7 to 36 months.	0.78
Koolen *et al.* (2005)				9	Not specified/reported	100% global developmental delay.	0.56
Luciani *et al.* (2003)				33	Not specified/reported	100% global developmental delay	0.33

Reference	Quality Criteria: Sample	Quality Criteria: Syndrome	Quality Criteria: Characteristic	N	Assessment/measure	Findings	Quality Rating
Manning *et al.* (2004)				11	Clinician judgement	100% global developmental delay.	0.67
Mieses *et al.* (2016)				24	Not specified/reported	100% low intellectual functioning.	0.44
Nesslinger *et al.* (1994)				7	Clinician judgement	100% developmental delay.	0.56
Oberman *et al.* (2015)				40	Vineland Adaptive Behaviour Scales	100% obtained scores suggestive of global cognitive deficit 52.5% mild adaptive behaviour delay 42.5% moderate adaptive behaviour delay.	0.44
Phelan *et al.* (2001)				37	The Battelle Developmental Inventory Vineland Adaptive Behavior Scales Parental report	100% global developmental delay 75% severe to profound mental retardation 25% mild to moderate mental retardation.	0.67
Philippe *et al.* (2008)				8	Psycho-Educational Profile-Revised Wechsler Intelligence Scale for Children-III	88% mild to severe delay in all developmental milestones One participant assessed using Wechsler Scale and IQ score was 60.	0.56
Reierson *et al.* (2017)				50	Stanford-Binet Intelligence Scales-IV or Mullen Scales of Early Learning	59% severe to profound ID.	0.44
Sarasua *et al.* (2011)				71	Parental report	100% developmental delay ranging from mild to profound	0.56

Reference	Quality Criteria: Sample	Quality Criteria: Syndrome	Quality Criteria: Characteristic	N	Assessment/measure	Findings	Quality Rating
Shaw *et al.* (2011)				35	Parental report of previous assessments Vineland Adaptive Behavior Scale-II	100% severe to profound IQ 100% low to very low adaptive behaviour.	0.67
Soorya *et al.* (2013)				32	Mullen Scales of Early Learning Stanford-Binet Intelligence Scales-IV Leiter International Performance Scale-R Vineland Adaptive Behavior Scales-II	10% mild ID 10% moderate ID 23.3% severe ID 53.3% profound ID.	0.89
Wang *et al.* (2016)				11	Vineland Adaptive Behavior Scale-II	100% developmental delay.	0.67
Wilson *et al.* (2003)				56	The Developmental Profile- II The Scales of Independent Behaviour-Revised - Full Scale	100% moderate to profound IQ Mean age equivalent between 14.2 months to 19.7 months	0.56
Zwanenburg *et al.* (2016)				33	The Bayley Scales of Infant and Toddler Development-III, adapted and validated for the Dutch population Wechsler Preschool and Primary Scale of Intelligence-III, Dutch version Vineland Screener 0–6 years	100% global developmental delay Maximal age equivalents of 34 to 38 months One child assessed with the Wechsler Scale and found to have a cognitive age equivalent of 52 months.	0.78

Speech and Language

Findings associated with speech and language were identified in 18 papers. Results are displayed in Table 5. Overall, speech and language abilities were reported to be delayed. The number of participants reported ranged from 7-201. Sarasua, Boccuto *et al.* (2014) reported on the largest sample (N=201), relying on parental report to measure speech and language abilities of participants.

Of those identified, seven received good overall quality ratings (Denayer *et al.*, 2012; Dhar *et al.*, 2010; Manning *et al.*, 2004; Rankine *et al.*, 2017; Soorya *et al.*, 2013; Wang *et al.*, 2016; Zwanenburg *et al.*, 2016). All participants within this selection of studies displayed delayed or absent speech. Over half utilised direct in-person assessments including the Mullen Early Learning Scale (Mullen, 1995) and the Bayley Scales of Infant and Toddler Development (Bayley, 2005). Age equivalents were also discussed by Wang *et al.* and Zwanenburg *et al.* to demonstrate the extent of speech delay. Wang *et al.* also used a comparison group of children with idiopathic ASD to show that a PMS group were significantly more impaired in relation to speech.

Table 5. Summary of studies reporting on speech and language in PMS

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristic	N	Assessment/measure	Findings	Quality Rating
Denayer *et al.* (2012)				7	Parental report/observation	100% language development severely delayed 14% spoke in short sentences 43% used single words 43% displayed no speech.	0.67
Dhar *et al.* (2010)				13	Not specified/reported	100% speech delay and/or loss of speech.	0.67
Egger *et al.* (2016)				7	Vineland Screener	100% profound communication deficits, with limited expressive and receptive language 14% absent speech 29% virtually absent 57% simple sentences.	0.56
Koolen *et al.* (2005)				9	Not specified/reported	100% absent or severely delayed speech.	0.56
Luciani *et al.* (2003)				33	Not specified/reported	100% mild to very severe expressive speech delay.	0.33
Manning *et al.* (2004)				11	Clinician judgement	100% severely delayed speech or absent speech.	0.67
Nesslinger *et al.* (1994)				7	Clinician judgement	100% delays or absence of expressive speech 43% used no words 43% described as babbling 14% used < 10 words.	0.56

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristic	N	Assessment/measure	Findings	Quality Rating
Oberman *et al.* (2015)				40	ADI-R	75% non-verbal.	0.56
Phelan *et al.* (2001)				37	Clinician judgement	100% absent/severely delayed speech.	0.44
Philippe *et al.* (2008)				8	Unclear	100% delayed language development, ranging from total absence to functional language with minor pronunciation difficulties.	0.33
Rankine *et al.* (2017)				18	Mullen Scales of Early Learning Vineland Adaptive Behavior Scales MacArthur-Bates Communicative Developmental Inventories	100% major language delay 28% single word speech.	0.78
Sarasua, Boccuto *et al.* (2014)				201	Medical history questionnaire by parents – unspecified	100% speech delay 36% no speech 19% vocabulary < 40 words 7% used > 50 words and had the ability to use phrases 9% had large vocabularies and used full sentences.	0.56
Sarasua, Dwivedi *et al.* (2014)				70	Medical history questionnaire by parents – unspecified	100% speech delay 34% absent speech 20% minimal speech 16% used sentences.	0.56
Sarasua *et al.* (2011)				71	Medical history questionnaire by parents – unspecified	100% absent or delayed speech 35% spoke no words 29% spoke > 40 words 15% spoke in sentences.	0.56

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristic	N	Assessment/measure	Findings	Quality Rating
Soorya *et al.* (2013)				32	Clinician judgement Vineland Adaptive Behavior Scale Mullen Scales of Early Learning	100% delayed language ability 16% used some words spontaneously to communicate on a regular basis.	0.89
Wang *et al.* (2016)				11	Mullen Scales of Early Learning	100% nonverbal or minimally verbal Receptive language age equivalent mean score of 14 months Expressive language age equivalent of 11 months.	0.78
Wilson *et al.* (2003)				56	Examination of medical records	100% severely impaired expressive speech.	0.44
Zwanenburg *et al.* (2016)				33	The Bayley Scales of Infant and Toddler Development-III, adapted and validated for the Dutch population	Maximal age equivalent for receptive and expressive language 34 months.	0.78

ASD and Autistic Features

Fifteen papers reported on ASD and features associated with ASD (thirteen on ASD and five on autistic features). Findings are displayed in Table 6. The number of participants reported within studies ranged from 7-127. Sarasua, Boccuto *et al.* (2014) represented the largest sample. Philippe *et al.* (2008) was the only paper to report that no participants met the criteria for Autistic Disorder, whilst reporting that all displayed impairments in social interaction and communication, and quality was lower primarily due to poor sample identification.

Ten of the identified papers obtained a quality rating of 0.67 or above (Denayer *et al.*, 2012; Dhar *et al.*, 2010; Kolevzon *et al.*, 2014; Manning *et al.*, 2004; Mieses *et al.*, 2016; Phelan *et al.*, 2001; Rankine *et al.*, 2017; Shaw *et al.*, 2011; Soorya *et al.*, 2013; Wang *et al*., 2016). Eight of these papers reported on the diagnosis of ASD, and participants met criteria indicative of ASD range or received a clinical diagnosis of ASD in between 23% and 100% of participants. Five of these papers utilised diagnostic instruments with consensus from multiple assessments including versions of the Autism Diagnostic Observation Schedule (ADOS; Lord *et al.,* 2008), considered a gold-standard in assessments of ASD (Ozonoff *et al.*, 2005). Four participants obtained scores classified with Pervasive Developmental Disorder (Denayer *et al.*, 2012). Dhar *et al.* obtained the highest and maximum score for quality rating, indicating excellent sample identification, confirmation of PMS and behavioural assessment (as rated by quality criteria), although sample size was relatively small at 13.

Meta-analysis estimated pooled prevalence of ASD to be 51.3% (95% CI 32.7 to 69.7%) for the random effects model, and 50.4% (95% CI 30.2 to 70.6%) for the quality effects model. Forest plots for the random effects and quality effects models are shown in Figures 2 and 3.

Table 6. Summary of studies reporting on ASD and autistic features in PMS

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristic	N	Assessment/measure	Findings	Proportion meeting ASD criteria	Quality Rating
Denayer *et al.* (2012)				7	Scale of Pervasive Developmental Disorders in Mentally Retarded Persons	100% autistic-like behaviour including poor social reciprocity 57% classified with Pervasive Developmental Disorder 43% scored within the normal range.	0/7	0.78
Dhar *et al.* (2010)				13	ADOS ADI-R Gilliam and Childhood Autism Rating Scale	23% diagnosed with Autism 92% autistic-like features.	3/13	1.0
Kolevzon *et al.* (2014)				9	ADOS ADI-R DSM-5	100% met criteria for ASD.	9/9	0.78
Manning *et al.* (2004)				11	Clinician judgement	45% autistic like behaviours, including decreased socialisation, self-injurious behaviours and repetitive self-stimulatory actions.	0/11	0.67
Mieses *et al.* (2016)				24	ADOS DSM-5	92% met criteria for ASD.	22/24	0.78
Oberman *et al.* (2015)				40	Parental report ADI-R	53% diagnosed with ASD 90% displayed persistent deficits in social communication 55% displayed restricted, repetitive patterns of behaviour 73% displayed blunted facial expression.	21/40	0.56
Phelan *et al.* (2001)				18	The Childhood Autism Rating Scale	94% scored in the autistic range 94% mild-moderate range for ASD 67% severe range for ASD.	17/18	0.67

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristic	N	Assessment/measure	Findings	Proportion meeting ASD criteria	Quality Rating
Philippe *et al.* (2008)				8	ADI-R	0% fulfilled criteria for autistic disorder 100% displayed poor reciprocal social interaction, play and communication.	0/8	0.56
Rankine *et al.* (2017)				18	ADOS	94% met criteria for ASD 100% autistic traits.	17/18	0.67
Sarasua, Boccuto *et al.* (2014)				127	Medical history questionnaire by parents – unspecified	31% diagnosed with ASD 35% autistic like behaviours.	39/127	0.56
Sarasua, Dwivedi *et al.* (2014)				52	Medical history questionnaire by parents - unspecified	25% diagnosed with ASD	13/52	0.56
Sarasua *et al.* (2011)				53	Parental report	26% diagnosed with ASD	14/53	0.56
Shaw *et al.* (2011)				35	Parent Form of the Children's Interview for Psychiatric Symptoms	31% diagnosed with ASD	11/35	0.67

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristic	N	Assessment/measure	Findings	Proportion meeting ASD criteria	Quality Rating
Soorya *et al.* (2013)				32	ADOS ADI-R DSM-IV	75% met criteria for Autism 9% Autism Spectrum 16% did not meet criteria for an ASD. Repetitive behaviours were commonly displayed: unusual sensory interests (n = 21), repetitive use of objects (n = 19), hand and finger motor mannerisms (n = 13), circumscribed interests (n = 11) and negative reactions to changes in personal routines (n = 10).	27/32	0.89
Wang *et al.* (2016)				11	ADOS ADI-R DSM-5	100% met criteria for Autism 91 % met criteria for ASD.	11/11	0.89

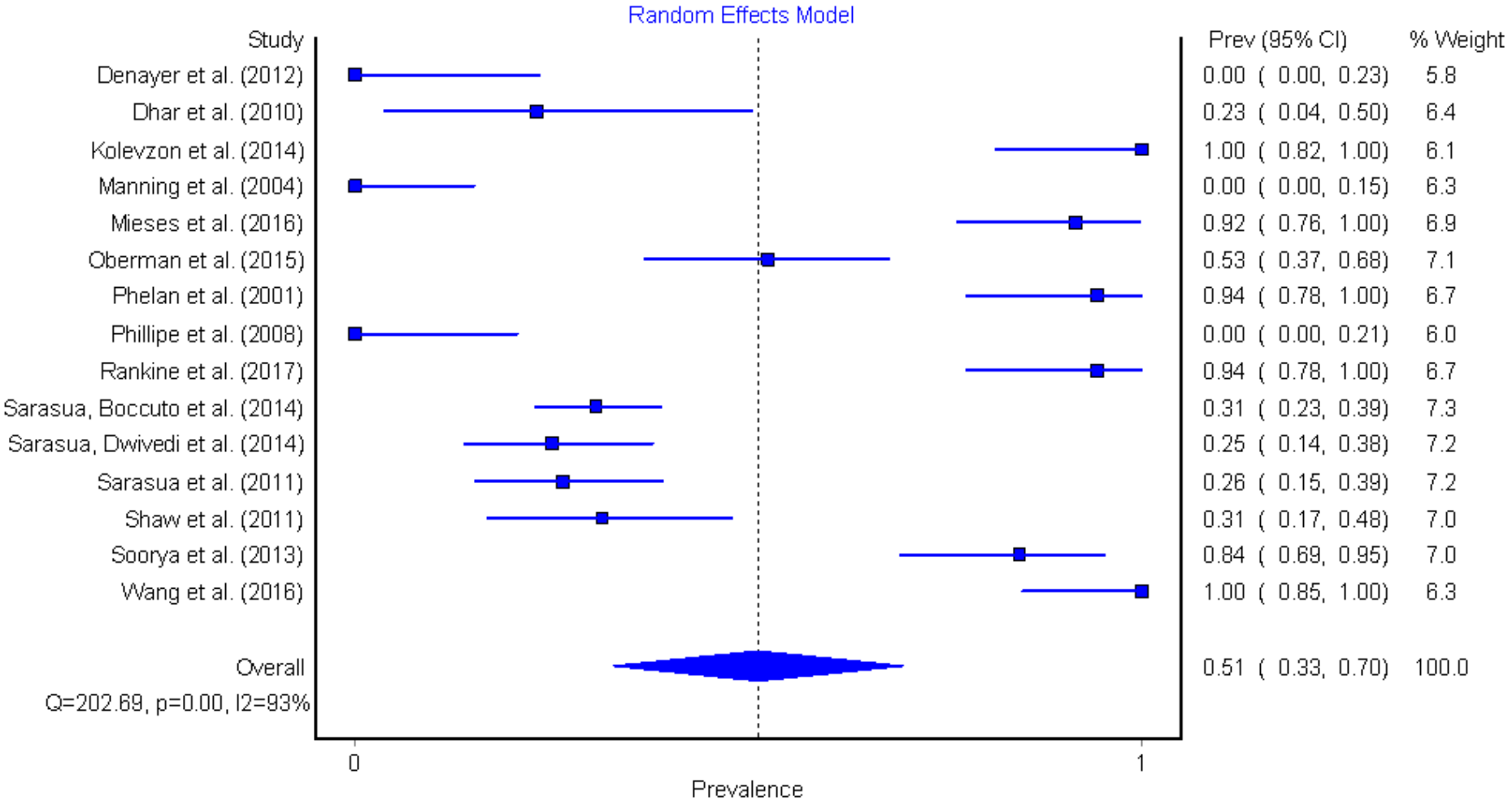

Figure 2: Forest plot of pooled prevalence estimates of ASD using a random effects model

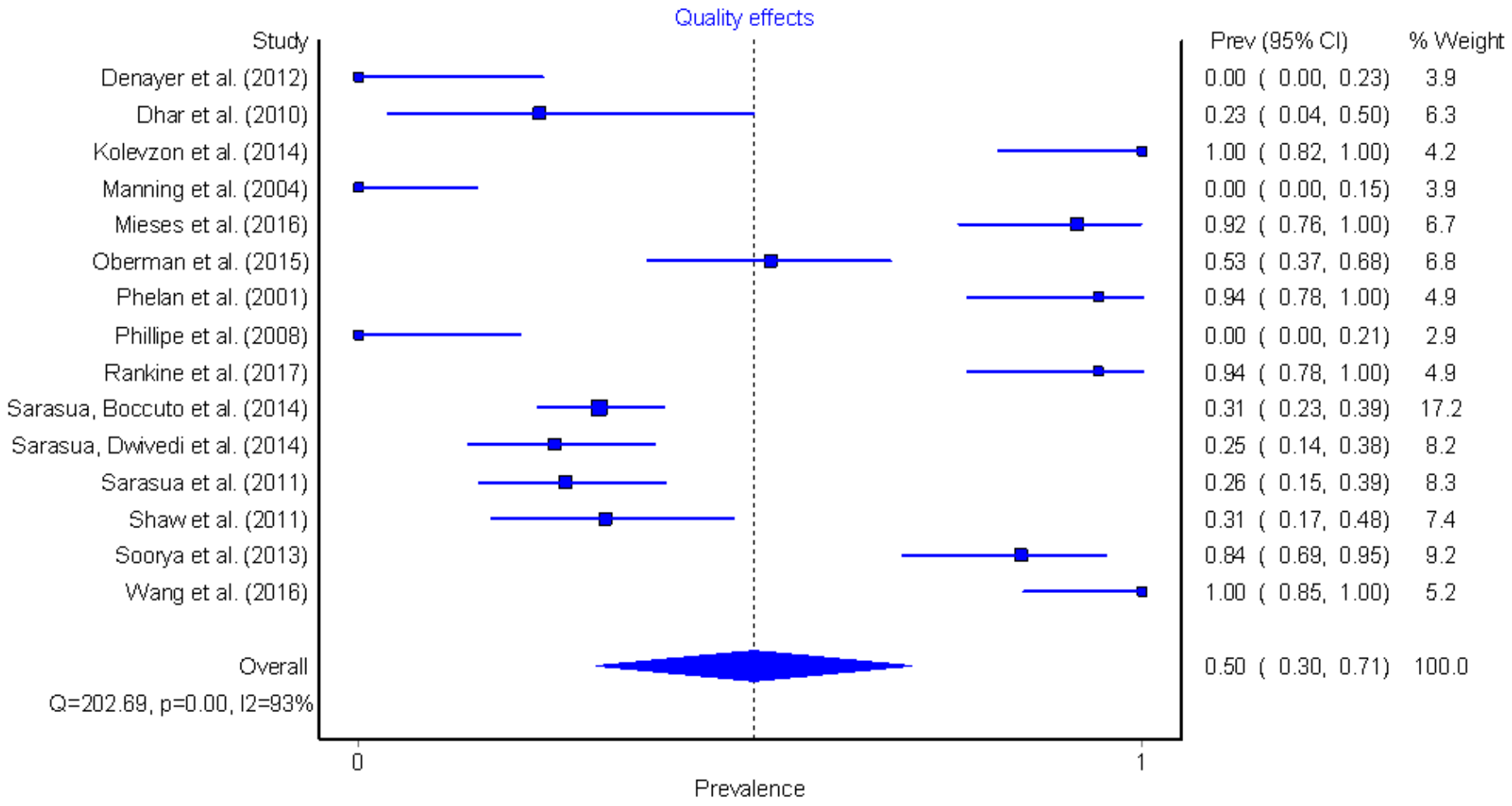

Figure 3: Forest plot of pooled prevalence estimates of ASD using a quality effects model

Behavioural Features

Data on behavioural difficulties in PMS were reported in ten papers (Table 7). The behaviours named within studies included terms such as restlessness, in two papers, and aggression, in six papers. The majority of studies used assessment measures with unestablished questionable reliability/validity, such as informal observation or parental report (classified as 'poor' on the quality appraisal tool). The number of participants reported ranged from 7-127.

Only four studies reached 0.67 or above on quality assessment (Denayer *et al.*, 2012; Dhar *et al.*, 2010; Shaw *et al.*, 2011; Soorya *et al.*, 2013). While behavioural problems were highlighted, a variety of terms were used to describe different forms of challenging or disruptive behaviour. Aggressive behaviour was highlighted in two of these (Shaw *et al.*, 2011; Soorya *et al.*, 2013).

Table 7. Summary of studies reporting on behavioural features in PMS

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristic	N	Assessment/measure	Findings	Quality Rating
Denayer *et al.* (2012)				7	Developmental Behaviour Checklist	100% severe challenging behaviour including "self-absorbing" behaviour, problems with social relating and disruptive behaviour.	0.78
Dhar *et al.* (2010)				13	Clinician Judgement	92% behavioural problems including restlessness and self-stimulation.	0.67
Luciani *et al.* (2003)				33	Not specified/reported	97% behavioural problems including aggressive outbursts.	0.33
Philippe *et al.* (2008)				8	Unclear	100% behavioural problems including restlessness and resistance to change.	0.33
Sarasua, Boccuto *et al.* (2014)				127	Medical history questionnaire by parents – unspecified	39% aggressive behaviour Participants displayed hair pulling, screaming and impulsiveness.	0.56
Sarasua, Dwivedi *et al.* (2014)				59	Medical history questionnaire by parents – unspecified	34% aggressive behaviour. Participants displayed hair pulling and pinching.	0.56
Sarasua *et al.* (2011)				60	Parental report	33% aggressive behaviour.	0.56
Shaw *et al.* (2011)				35	Vineland Adaptive Behavior Scale-II Parent Form of the Children's Interview for Psychiatric Symptoms	100% behavioural problems 31% impulsive 46% irritable or aggressive Elevations in internalising and externalising behaviours.	0.67

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristic	N	Assessment/measure	Findings	Quality Rating
Soorya *et al.* (2013)				32	Parent interview Clinical Judgement Vineland Adaptive Behaviour Scales	44% aggressive or self-injurious Elevations in internalising and externalising behaviours.	0.67
Wilson *et al.* (2003)				56	Maladaptive Behaviour Index Profile	Participants found to have fewer maladaptive behaviours than other children of a similar level of cognitive ability Scores indicated a normal level of problematic behaviour.	0.56

Motor Skills

Data on motor skills were reported in nine papers (Table 8). Delayed development of motor skills was evidenced in six papers, while two merely stated participants learnt to walk after 15 months. The number of participants reported in these studies ranged from 7-146. Only three were assessed as having quality of 0.67 or above (Denayer *et al.*, 2012; Soorya *et al.*, 2013; Zwanenburg *et al.*, 2016). Within this sample, some participants were mobile and able to walk independently, while others displayed difficulties with motor coordination. Papers appeared to provide little additional detail or description and therefore the exact comparison of findings may be difficult.

Table 8. Summary of studies reporting on motor skills in PMS

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristics	N	Assessment/measure	Findings	Quality Rating
Denayer *et al.* (2012)				7	Parental report/observation	71% mobile 14% wheelchair bound 14% bedridden.	0.67
Egger *et al.* (2016)				7	Vineland screener	71% delayed motor development Age equivalent scores ranged from 1.7-7.9 years.	0.56
Nesslinger *et al.* (1994)				7	Clinician judgement	100% delay of gross motor milestones.	0.56
Philippe *et al.* (2008)				8	Unclear	100% impaired fine and gross motor skills.	0.33
Sarasua, Boccuto *et al.* (2014)				146	Medical history questionnaire by parents – unspecified	88% could walk independently by the age of 3 years.	0.56
Sarasua, Dwivedi *et al.* (2014)				45	Medical history questionnaire by parents – unspecified	80% learned to walk later than 15 months.	0.56
Sarasua *et al.* (2011)				46	Parental report	80% learnt to walk later than 15 months.	0.56
Soorya *et al.* (2013)				16	Neurological examination Mullen Scales of Early Learning Vineland Adaptive Behavior Scale	94% gait abnormal including wide based stance and in-toeing 88% abnormal motor coordination Participants performed in the 14 to 19-month range.	0.89

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristics	N	Assessment/measure	Findings	Quality Rating
Zwanenburg *et al.* (2016)				33	The Bayley Scales of Infant and Toddler Development-III, adapted and validated for the Dutch population	Ability to walk independently acquired between 12 and 96 months of age. Maximal age equivalent for fine and gross motor domains were 35 and 33 months.	0.78

Sleep Difficulties

Data on sleep difficulties were reported in four papers (Table 9). The study by Bro *et al.* (2017) directly focused on sleep and recruited a large sample, providing detailed data on participants who displayed sleep disturbance and had been diagnosed with a sleep disorder. Comparisons were also made to community samples to display the elevation of scores. However, the quality rating was low due to a parent questionnaire being utilised and no molecular confirmation of PMS. Two studies obtained higher quality ratings (Dhar *et al.*, 2010; Soorya *et al.*, 2013) and between 41% and 46% of participants in these two studies displayed sleep disturbances.

Table 9. Summary of studies reporting on sleep in PMS

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristics	N	Assessment/measure	Findings	Quality Rating
Bro *et al.* (2017)				193	Children's Sleep Habits Questionnaire	90% marked sleep disturbance 17% diagnosed sleep disorder 35% took sleep medication Participants struggled with sleep initiation, maintenance and demonstrated behaviours associated with various parasomnias.	0.33
Dhar *et al.* (2010)				13	Clinician judgement	46% marked sleep disturbance.	0.67
Sarasua, Boccuto *et al.* (2014)				26	Medical history questionnaire by parents – unspecified	46% sleep problems.	0.56
Soorya *et al.* (2013)				32	Parent report Clinician judgement Vineland Adaptive Behavior Scale	41% marked sleep disturbance.	0.67

Mental Health

Three papers reported on aspects of mental health, with reference to traditional psychiatric diagnoses of bipolar disorder and affective disorder. Results are displayed in Table 10. All three papers obtained a good quality rating. Results appeared to vary in relation to the proportions of bipolar and affective disorder as it was reported in between 6% and 86% of participant samples. There did not appear to be a consistent method used in assessing for this, with observation, parental interviews and one direct assessment being used.

Table 10. Summary of studies reporting on mental health in PMS

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristics	N	Assessment/measure	Findings	Quality Rating
Denayer *et al.* (2012)				7	Parental report Observation	57% Bipolar Disorder.	0.67
Egger *et al.* (2016)				7	Psychopathology Inventory of Mentally Retarded Adults	86% Affective Disorder 43% anxiety.	0.67
Shaw *et al.* (2011)				35	Parent Form of the Children's Interview for Psychiatric Symptoms	6% Bipolar Disorder.	0.67

Attention and Hyperactivity

Attention Deficit Hyperactivity Disorder (ADHD) and characteristics associated with this were discussed in three papers. Findings are displayed in Table 11. Of those with higher quality ratings (Denayer *et al.*, 2012; Shaw *et al.*, 2011), results varied with between 14% and 34% of participants having a diagnosis of ADHD which had been determined through parental report or parent informed interviews.

Table 11. Summary of studies reporting on attention and hyperactivity in PMS

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristics	N	Assessment/measure	Findings	Quality Rating
Denayer *et al.* (2012)				7	Parental report Observation	14% ADHD 29% ADHD symptoms	0.67
Shaw *et al.* (2011)				35	Parent Form of the Children's Interview for Psychiatric Symptoms.	34% ADHD.	0.67
Soorya *et al.* (2013)				32	Clinician judgement	50% exhibited hyperactivity.	0.56

Additional Characteristics

In addition, a small number of studies also reported on sensory experiences and high pain threshold, while quality ratings for these appeared quite low and no studies reached ratings of > 0.67. This seemed largely due to the assessment instruments used to measure these characteristics (see Table 12 and 13).

Table 12. Summary of studies reporting on sensory experiences in PMS

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristics	N	Assessment/ measure	Findings	Quality Rating
Mieses *et al.* (2016)				24	Sensory profile	80% sensory reactivity abnormalities	0.56
Philippe *et al.* (2008)				8	Unclear	100% sensory processing abnormalities, unusual responses to environment and sensory stimuli.	0.33
Sarasua, Boccuto *et al.* (2014)				175	Medical history questionnaire by parents – unspecified	46% overly sensitive to touch.	0.56
Sarasua, Dwivedi *et al.* (2014)				59	Medical history questionnaire by parents – unspecified	64% overly sensitive to touch.	0.56

Table 13. Summary of studies reporting on high pain threshold in PMS

Reference	Quality criteria: Sample	Quality criteria: Syndrome	Quality criteria: Characteristics	N	Assessment/measure	Findings	Quality Rating
Phelan *et al.* (2001)				37	Observation	86% high pain threshold.	0.44
Sarasua, Boccuto *et al.* (2014)				170	Medical history questionnaire by parents – unspecified	77% high pain threshold.	0.56
Soorya *et al.* (2013)				32	Review of medical records	88% high pain threshold.	0.56

Relationships between variables

In several of the papers relationships between behavioural/psychological characteristics and genetics were reported, e.g. severity of DD/ID reportedly increased in proportion to deletion size (Luciani *et al.*, 2003; Sarasua *et al.*, 2011; Wilson *et al.*, 2003; Zwanenburg *et al.*, 2016). Sarasua, Dwivedi *et al.* (2014) also indicated specific deletion breakpoints associated with speech ability, and ASD and aggressive behaviour were associated with smaller deletions. Similar findings were found by Sarasua *et al.* (2011) who reported median deletion size was higher for participants with absent speech, and more ASD and aggressive behaviour with smaller deletions. In contrast, Soorya *et al.* (2013) found larger deletion sizes were associated with ASD, while others found no relation between clinical features and deletion size (Koolen *et al.*, 2005). In addition, Oberman *et al.* (2015) conducted correlations and reported more severe restricted and repetitive behaviours were associated with small deletion sizes, while larger deletions were associated with greater impairment in adaptive behaviour skills.

Assessment of relationships between behavioural characteristics was more limited. Phelan *et al.* (2001) and Philippe *et al.* (2008) reported a positive relationship between developmental/cognitive scores and Autism assessments. Shaw *et al.* (2011) investigated differences between participants with and without ASD and identified significant differences between the exact set of maladaptive behaviours displayed (e.g. in refusing to respond and becoming obsessed with certain objects).

1.5 Discussion and Conclusions

This systematic literature review aimed to identify, synthesise and critically appraise research on behavioural and psychological characteristics associated with PMS. Data were presented from 57 eligible studies. A variety of behavioural and psychological characteristics were discussed within these studies. Quality of the identified research was assessed using an adapted published quality appraisal tool.

1.5.1 Summary of Main Results

The frequency of findings varied slightly between research using a case study and a cohort methodology, although DD/ID of varying degrees, and delayed speech, were reported frequently in both types of paper. ASD and autistic features and psychomotor delay were also reported/assessed frequently. Other characteristics were reported in a smaller number of papers, including behaviours that challenge, sleep difficulties and types of mental health problems.

Clinical Features

The most frequently reported characteristics were DD/ID and delayed speech across both case studies and cohort studies. Within the cohort studies, papers with a higher quality rating found all participants displayed some level of DD and delayed or absent speech, confirming these as features of the behavioural phenotype of PMS. Regarding ASD, case studies tended to more commonly report on autistic features only in 42% of participants, where descriptions included poor eye contact, social communication and interaction. Of the cohort papers reporting on ASD, over half obtained a high-quality rating and a pooled prevalence was estimated at over 50%. The estimate exceeds estimates for the majority of genetic syndromes with established associations with ASD, as reported by Richards *et al.* (2015) (e.g., 16% for Down syndrome, 34% for Angelman syndrome, 35% for tuberous sclerosis complex), with the exception of Rett (61%) and Cohen's (54%) syndromes. It is important to note the wide confidence intervals of this estimate however (between approx. 30% and 70% for both models) which reflects the wide variability in studies' reported prevalence. This variability indicates that the literature is incredibly heterogenous and given this, the pooled prevalence estimates do need to be interpreted with some caution. Possible reasons for

the variability may be the variety of different tools and different methods utilised within the studies in assessing for ASD, with a proportion using the ADOS and the ADI-R, while others predominantly used parental report. For this review, it was important to include all relevant studies to evaluate the literature. However, future reviews could seek to determine more stringent inclusion criteria or categorise by assessment tools, to improve the internal validity of any future prevalence estimates. The implications of the variability may be that a diagnosis of ASD is appropriate in some cases, while it may not be evident in others. Overall, the findings suggest that an ASD profile seems likely to be associated with the behavioural phenotype of PMS, although the specific profile of ASD-related characteristics associated with this syndrome remains poorly elucidated and awaits further research. In addition, future research is required to clarify more accurately the prevalence of ASD in PMS. Data on delayed motor development were reported more frequently in case study papers, affecting 81% of cases overall in these studies. Within cohort studies reporting on motor development quality ratings were low. Reasons for this may include a limited availability of assessment instruments and therefore the more likely use of clinician judgment. Behavioural problems (e.g. aggression), sleep difficulties, mental health diagnoses (e.g. bipolar disorder) and attention and hyperactivity were each reported in a smaller number of case study and cohort study papers and fewer papers obtained higher quality ratings. In total, 24 papers reported on behavioural problems, 13 on sleep difficulties, 10 on aspects of mental health and 10 on attention and hyperactivity. Existing studies indicate that these characteristics may be prevalent in people with PMS (e.g., 41% - 90% of people were estimated to have some form of sleep disturbance in the cohort studies; the study (Egger *et al.*, 2016) reporting on 'affective disorder' reported it in 86% of participants) but they have not been extensively researched, therefore more research is likely to be needed to make firmer conclusions about the exact nature as well as the prevalence of these characteristics in PMS. Methodological limitations and differences between studies also created difficulties which meant it was problematic to compare and reliably synthesise findings (see below).

Genetic Features

Most papers provided genetic confirmation of the diagnosis of PMS and offered detailed genetic descriptions. A small number of papers did not directly confirm diagnosis using molecular/cytogenetic/metabolic techniques, while others reported on previous diagnoses or assessments. Confirmation of genetic diagnoses is fundamental in exploring the behavioural phenotype of PMS and other genetic conditions, to ensure internal validity. Detailed consideration of the relationship between genetic and behavioural features of PMS is beyond the scope of the current review. However, given the complex emerging picture of the variety of genetic atypicalities associated with PMS (including frequent but non-universal involvement of SHANK3, and possible roles for a number of other nearby genes), analysis of behavioural differences and similarities between genetic subtypes is an important area for future research. Four papers in this review (Luciani *et al.*, 2003; Sarasua *et al.*, 2011; Wilson *et al*., 2003; Zwanenburg *et al.*, 2016) found that deletion size was positively associated with severity of developmental delay, while there were contrasting results regarding deletion size and ASD, and other studies reported no relation between clinical features and deletion size (Koolen *et al.*, 2005). This reveals a complex picture. Whilst results of molecular genetic analysis were available in the majority of papers reviewed, and the syndrome was genetically confirmed in almost all cases, the genetic detail presented about each case varied. Genetic underpinnings of the syndrome varied widely between cases, with variations in SHANK3 involvement, although only eight papers assessed the relationship between genetic variants and behavioural outcomes.

1.5.2 Methodological Features

There were numerous methodological limitations within the studies reviewed. The research designs used were cohort and case study methodologies which have their own advantages and limitations. A higher proportion of papers identified in this review used a case study methodology and although these can offer in-depth descriptions of individual presentations, they had small sample sizes and were generally reliant on clinical judgment without formal comparisons, limiting generalisation. Cohort studies on the other hand offer larger samples and increased generalisability. The cohort studies identified offered sample sizes of 7-201 in this review, therefore recruitment on

a larger scale may be beneficial in future research. In addition, possible effects of genetic and other variability may be occluded by amalgamating data from numerous people.

Methodological issues included participant recruitment and selection, with recruitment often being from clinics and national and regional parent support groups. People may be more likely to be part of a support group, or to complete or volunteer if they are experiencing problems or difficulties, which may bias results. This can lead to selection bias and impacts on the representativeness of findings. Denayer *et al.* (2012), Dhar *et al.* (2010) and Manning *et al.* (2004) utilised random sampling techniques via ID populations and where PMS was not suspected before genetic assessment, which naturally leads to a low N, and also means that participants have ID by definition. The recruitment of larger samples through different sources is likely to improve validity and generalisability. Although the age range in this review encompassed papers reporting on participants up to the age of 70 years old, there was a focus on samples of children with cross sectional design, meaning that behavioural and psychological development across the lifespan remain relatively uncharacterised.

Use of standardised measures improved reliability and validity of findings, however inherent challenges of assessing and measuring various characteristics in individuals with ID create obstacles in making meaningful conclusions. The applicability of certain assessments and diagnostic categories for people with ID (e.g., assessments of mental health difficulties) is often unclear, which can limit conclusions. For instance, given that findings indicated that delayed speech appears to be associated with PMS, some measures may not accurately allow individuals to describe their thoughts and feelings or make attributions in the same way as people without PMS. This is a common difficulty in research in the field of neurodevelopmental conditions with associated ID and the development of measures specifically for people with ID is invaluable. Many of the measures were also based on parental report. Although parental questionnaires can allow large samples to be collected and increase accessibility, they rely on accurate and retrospective reporting without direct assessment. Frequently, studies did not provide detailed descriptions, for example not distinguishing between categories assigned to developmental level and ID or absent and delayed speech. This resulted in behavioural

descriptions at a relatively gross level. The variety of different assessment measures, and idiosyncratic use of categorisation also poses some difficulty in synthesis of results. Mulder *et al.* (2016) highlight this within a systematic review into behaviour associated with Cornelia de Lange syndrome and they put forward the case for more consistent assessment instruments being used to allow for such comparisons to be made.

A lack of comparison groups also poses an obstacle in being able to elucidate behavioural phenotypes, since comparison with other groups matched on key variables such as developmental level has been highlighted as crucial to the process (Dykens, 1995). Comparison groups are valuable in improving research into behavioural phenotypes. Use of comparison groups was particularly uncommon within the identified papers. Three studies referred to some comparison of previously completed studies on PMS (Phelan *et al.*, 2001; Reierson *et al.*, 2017) or typically developing controls (Bro *et al*., 2017). While only Glaser and Shaw (2011), Mieses *et al.* (2016) and Wang *et al.* (2016) used more defined comparison groups of children with ASD. This is imperative within research into behavioural phenotypes to elucidate levels of specificity of behavioural characteristics to PMS.

1.5.3 Clinical Implications and Directions for Future Research

The findings of the review have implications for practice. Based on the results of this review, individuals with PMS are likely to present with developmental delay and delayed speech development and it would be imperative for clinicians and families to be aware of this. Following diagnosis of PMS, it may be valuable to carry out comprehensive assessments in relation to developmental level, speech and communication and ASD, with repeated follow-ups as necessary to assess interventions that may be helpful or adaptations that can be made. The results relating to ASD also suggest that characteristics associated with this may be prevalent, although wide variability in the pooled prevalence results suggest this isn't always the case. This would suggest that individuals with PMS would benefit from a detailed assessment of ASD impairments. Resources targeted at supporting developmental delay and speech difficulties are likely to be effective and therefore it may be helpful for clinicians to signpost or refer individuals to additional sources of support, for example speech and language therapy. Given the range of characteristics discussed in this review, clinicians

should also keep in mind the variability of clinical features that may present in individuals with PMS, monitoring these characteristics during initial assessment and during check-ups.

Future research is required to investigate more nuanced elements of the behavioural phenotype of PMS and predictors of variability in presentation. It would be valuable for future research to use larger samples with cohort designs to reduce the focus on case studies. Standardised assessment instruments and appropriately matched comparison groups would also increase accuracy and reliability, as well as offering more detailed analysis. A more detailed investigation of ASD and PMS would be helpful to support clarification of the prevalence of this and delineation of the exact profile of ASD phenomenology associated, given the variability in results in the current review. In addition, given the less frequent study of characteristics such as behavioural problems, sleep difficulties, mental health and ADHD, it would be beneficial for future research to investigate these characteristics more thoroughly to determine the prevalence of these characteristics further. Longitudinal research would also support the development of knowledge of development over time.

1.5.4 Strengths and Limitations

A strength of this review is that it identified and reviewed a large number of papers, synthesising and evaluating the findings and methodologies presented. A further strength was the use of a quality appraisal tool specifically developed for use in this type of research.

It should be noted that whilst every effort was made to ensure all papers related to PMS and behaviour were identified and screened, using a variety of search terms for PMS and seeking consultation from a clinical and academic psychologist with expertise in the area, it remains possible that, due to advances in knowledge of the genetic makeup of PMS in recent years, variations may have been missed. In addition, only four databases were searched so it is difficult to eradicate the possibility that other sources may have contained other relevant papers. Only English language and published papers were screened which presents a possible risk of bias. Due to the rarity of the syndrome in question, some authors were found to utilise participant samples from ongoing research

studies, Phelan *et al.* (2001) acknowledged that five of their participants had been involved in other research, and Reierson *et al.* (2017) reported some participants had been recruited previously by Soorya *et al.* (2013), therefore it is possible that some of the papers may be reporting on a repeated sample of individuals, or at least that some cross over is likely.

1.5.5 Concluding Remarks

To conclude, this systematic review aimed to present an overview of the research on the behavioural and psychological characteristics of PMS. From reviewing the literature, it is clear there are a number of commonly reported behavioural and psychological characteristics associated with PMS. However, the results show that methodological differences and limitations present a challenge in bringing results together. It appears that PMS may have an emerging behavioural phenotype while more robust research is required to ascertain this exactly. This would contribute to the understanding of PMS, genetic conditions and the literature available on behavioural phenotypes.

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PART 2: RESEARCH REPORT

Behavioural and psychological characteristics and difficulties associated with Sotos syndrome in adolescence/adulthood: A follow-up study

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Target Journal: American Journal of Medical Genetics

Behavioural and psychological characteristics and difficulties associated with Sotos syndrome in adolescence/adulthood: A follow-up study

Lisa Humphries

2.1 Abstract

Background: Whilst research into the behavioural and psychological characteristics of Sotos syndrome has been growing in recent years, little is known about how the behaviour of people with Sotos develops as they grow older. This study provides a seven-year follow-up of behavioural characteristics of participants reported by Sheth *et al*. (2015). It further characterises adaptive ability, and conducts assessment of mood-related difficulties in a group of people with Sotos syndrome.

Methods: Parents and carers of 36 individuals with Sotos syndrome who took part in the study reported by Sheth *et al*. (2015) were invited to take part. Fifteen participated and completed online questionnaires and a telephone interview, measuring adaptive behaviour, impulsivity, repetitive behaviour, challenging behaviour, mood and social communication, all of which had been completed during the previous study. Additional measures of adaptive behaviour, mood and sensory processing were also conducted.

Results: Results indicated significant reductions in impulsivity and overactivity. Frequency of meeting criteria indicative of Autism Spectrum Disorder (ASD) decreased, with significantly fewer impairments with reciprocal social interaction. Differences in other characteristics over time were not statistically significant but may warrant further investigation. High proportions of participants continued to engage in repetitive questioning (86.7%) and showed preference for routine (73.3%). 40% displayed behaviour indicative of sensory hyporesponsiveness. Anxiety was prevalent, with peaks in panic, obsessive-compulsive behaviour and social avoidance.

Conclusions: Findings indicated different areas of possible stability and change. Indications of a specific profile of anxiety highlight the need for future research in this area. Repeated monitoring and assessment of impulsivity, overactivity, ASD phenomenology and anxiety may be helpful for people with Sotos syndrome and their families.

Keywords: Sotos syndrome, behavioural phenotype, follow-up, anxiety

2.2 Introduction

Sotos syndrome is a genetic overgrowth condition first described in 1964 by Juan Sotos and colleagues (Sotos *et al.,* 1964). Overgrowth conditions are characterised by general or specific overgrowth in which individuals often have weight, height and/or head circumference that is significantly above average for their age and sex (Adam, 2014). These conditions are also associated with varying degrees of intellectual disability (ID; Min-Ko, 2013). Sotos syndrome is thought to affect approximately 1 in 14,000 people. Physical features associated with Sotos syndrome are characteristic facies[8], macrocephaly[9] and large stature (Veitch, n.d.). A systematic literature review indicated that most people with Sotos syndrome present with varying degrees of ID, ranging from very mild to very severe (Lane *et al.,* 2016b). Verbal ability is a relative strength while non-verbal reasoning is a relative weakness (Lane *et al.*, 2018). Sheth *et al.* (2015) investigated adaptive behaviour in Sotos syndrome and reported that 84% of their sample were able or partly able to carry out self-help skills; 89.5% were mobile (defined as able to walk independently upstairs and elsewhere) and 97.3% were verbal or partly verbal. Advanced bone age and growth also characterise the syndrome. Common health problems include epilepsy, scoliosis, neonatal hypotonia and congenital problems (Tatton-Brown & Rahman, 2004). Diagnoses are usually made based on physical appearance and genetic testing. Sotos syndrome is related to a mutation in the nuclear receptor set-domain-containing protein (NSD1) gene, although a minority of cases do not have this abnormality (Kurotaki *et al.,* 2002; Tatton-Brown *et al.,* 2005).

Genetic syndromes are often rare and therefore collective knowledge and understanding of the characteristics associated can be limited. Empirical research into behavioural phenotypes and characteristics associated with genetic syndromes has been advancing (Harris, 2002). This kind of research is thought to be of benefit to develop knowledge and understanding of specific syndromes, potentially leading to better outcomes and improve quality of life for individuals (Waite *et al.*, 2014). Research into the behavioural phenotype of Sotos syndrome has been growing, while a recent systematic review concluded that findings are restricted due to a lack of standardised assessment

[8] A condition defined by distinctive facial appearance.
[9] A condition where head circumference is disproportionately large.

measures and little use of comparison groups (Lane *et al.*, 2016b), with much research relying on case reports. Reported psychological and behavioural characteristics include Attention Deficit Hyperactivity Disorder (ADHD) and hyperactivity (e.g. Finegan *et al.,* 1994; Varley & Crnic, 1984), Autism Spectrum Disorder (ASD), social interaction difficulties and repetitive behaviours (e.g. Sarimski, 2003; Sheth *et al.*, 2015; Zappella, 1990), behavioural problems such as temper tantrums (e.g. Finegan *et al.,* 1994; Mouridsen & Hansen, 2002; Rutter & Cole, 1991) and deficits in speech and language (e.g. Ball *et al.*, 2005; Mauceri *et al.*, 2000; Patterson *et al.*, 1978), although systematic investigation of these behavioural characteristics remains rare.

Attention Deficit Hyperactivity Disorder

ADHD is characterised by symptoms of impulsivity, hyperactivity and difficulties in maintaining attention (Carr, 1999). Studies have directly discussed ADHD in people with Sotos syndrome with 16 out of 44 cases in the literature reported to have a diagnosis (Finegan *et al.*, 1994; Mauceri *et al.*, 2000; Varley & Crnic, 1984), while others have reported the presence of hyperactivity (Rutter & Cole, 1991; Varley & Crnic, 1984), impulsivity and overactivity (Sheth *et al.*, 2015). More detailed analysis has compared NSD1 mutation and non-mutation groups, with NSD1 mutation groups producing lower scores on hyperactivity measures and ADHD in one study (de Boer *et al.,* 2006). Sheth *et al.* (2015) reported participants with Sotos syndrome displayed a high level of impulsivity and overactivity which was comparable to those with idiopathic ASD. More in-depth investigation is needed to identify the exact nature of characteristics associated with impulsivity and hyperactivity in this group.

Autism Spectrum Disorder

ASD is a developmental condition defined by problems with social communication and interaction, as well as restricted/repetitive interests and behaviour. Studies have found relatively high proportions of people with Sotos syndrome meet criteria for a diagnosis, although assessment has often focused on clinical observation (Morrow *et al.*, 1990; Mouridsen & Hansen, 2002; Zappella, 1990). Using a screening tool, Sheth *et al.* (2005) found high levels of ASD in their sample, with 70.3% meeting the cut-off level for ASD and 32.4% meeting the cut-off level for Autism. Furthermore, people with

Sotos syndrome scored significantly higher on the social interaction domain than a Down syndrome (DS) group, while they scored significantly lower than an idiopathic ASD contrast group on the repetitive behaviour domain. The exact nature of ASD phenomenology (i.e., the sets of reasons people meet criteria for ASD diagnoses) can vary between genetic syndromes (Moss *et al.*, 2013), and to date there is little further investigation of the precise nature of ASD-related characteristics shown by this group. In addition, the DSM-V now includes sensory factors in the diagnostic criteria of ASD and therefore a better understanding of sensory characteristics of individuals with Sotos syndrome may be helpful to allow a more detailed characterisation of ASD phenomenology to be investigated. Differences in sensory experiences related to Sotos syndrome remain, to the author's knowledge, un-investigated. It may also be that characteristics associated with ASD are not static across the lifespan (e.g., there is some indication that characteristics of ASD become more pronounced with age for Cornelia de Lange syndrome (CdLS; Moss *et al.*, in press); one cross-sectional cohort study has reported that ASD phenomenology may differ with age with children showing more problematic signs of ASD than adults (Lane *et al.*, 2016$_a$)). Sheth *et al.* (2015) suggest that a longitudinal investigation of changes between ages would explore the trajectory more effectively.

Repetitive Behaviours

The term 'repetitive behaviours' encompasses a collection of behaviours including repetitive speech, insistence on sameness, obsessive and compulsive behaviour and stereotyped behaviour. The investigation of repetitive and ritualistic behaviour in Sotos syndrome has tended to rely upon clinical observation and unstructured parental report (Mourisden & Hansen, 2002; Rutter & Cole, 1991; Zapella, 1990), although standardised measures have also been completed by parents (Sarimski, 2003). In comparison to other syndromes (ASD, DS and Prader-Willi syndrome), Sheth *et al*. (2015) found significant differences with individuals with Sotos syndrome on subscale and total scores of the Repetitive Behaviour Scale (RBQ; Moss & Oliver, 2008; Moss *et al*., 2009). Individuals with Sotos syndrome displayed fewer stereotyped behaviours than the ASD group and higher levels of repetitive language than the DS group. At an item level, individuals with Sotos syndrome displayed peaks in repetitive questioning

and preference for routine, and it was noted that this was strikingly similar to the group with Prader-Willi syndrome (PWS). Sheth *et al.* also found that social impairments were a particular difficulty for people with Sotos syndrome and findings relating to social interaction difficulties have indicated that children with Sotos syndrome often tend to isolate themselves (e.g., Finegan *et al*., 1994; Rutter & Cole, 1991; Sarimski, 2003; Varley & Crnic, 1984; Zappella, 1990), although only two studies have utilised standardised measures and comparison groups (Finegan *et al*., 1994; Sarimski, 2003). More thorough assessment of repetitive behaviour and social interaction difficulties would support a more comprehensive understanding of these behaviours associated with Sotos syndrome and would also add to the knowledge of ASD-like characteristics seen in the syndrome.

Challenging Behaviours

The presence of challenging behaviours such as aggression and temper tantrums in Sotos syndrome has been reported in a number of studies (e.g., de Boer *et al.,* 2006; Finegan *et al.*, 1994; Mauceri *et al.*, 2000; Mouridsen & Hansen, 2002; Sheth *et al.,* 2015). Sheth *et al.* found that people with Sotos syndrome were more likely to display self-injurious behaviour, stereotyped behaviour and destruction of property than people with DS. However, research into behavioural issues has focused wholly on children and therefore little is known about how these behaviours persist with age and present into adulthood. Over half of the studies also used methods focusing on informal parental report or clinical observation and therefore the use of standardised assessments to delineate this further has been rare.

Anxiety

Anecdotal reports from parents/carers of people with Sotos syndrome have also indicated that anxiety can be problematic. Formal research into anxiety and Sotos syndrome has been rare, although de Boer *et al.* (2006) and Finegan *et al.* (1994) found that scores on the Child Behaviour Checklist (Achenbach, 1992) indicated significantly higher levels of anxiety and depression when compared to groups of people with ID of mixed aetiology. Differences within syndrome and between syndromes have also been found, with NSD1 mutation groups producing scores indicative of a more 'settled

mood' (de Boer *et al.,* 2006), while Sheth *et al.* (2015) found those with Sotos syndrome appeared to have greater pleasure and enjoyment in activities than those from an ASD group as assessed by the Mood, Interest and Pleasure Questionnaire (MIPQ-S; Ross & Oliver, 2008; Ross *et al.*, 2008). Sarimski (2003) also found children with Sotos syndrome became anxious when separated from their parents and in new situations using the Children's Social Behaviour Questionnaire (Luteijn *et al*., 1998) and the Nisonger Child Behavior Rating Form (Aman *et al.*, 1996), with overall higher anxiety subscale scores than typically developing children. Research has indicated that anxiety is particularly prevalent in certain genetic syndromes, and that different types of anxiety may be more problematic than others for individuals with different syndromes. For example, Crawford *et al.* (2017) found that people with CdLS obtained higher scores on separation anxiety and generalised anxiety subscales on the Spence Children's Anxiety Scale Parent Version (SCAS-P; Spence, 2000) than people with Fragile X (FXS) and Rubinstein-Taybi (RTS) syndromes. Further research is needed to more formally explore the nature of anxiety difficulties associated with Sotos syndrome, and to investigate whether a specific profile exists, which could ultimately help target interventions and indicate directions for future research.

Longitudinal Research

Little is known about how behaviours and characteristics associated with Sotos syndrome develop with age, and to the author's knowledge, only one study, of ten participants, has provided longitudinal data relating to cognitive ability (Bloom *et al.,* 1983), which suggested that intellectual abilities improved with age. Furthermore, much of the research into Sotos syndrome and associated characteristics has focused on children, an issue which also applies to research into many other genetic syndromes. Increased knowledge in this area is crucial to the development of the knowledge base of genetic syndromes. Cochran *et al.* (2015) carried out a two-and-a-half-year follow-up of the characteristics associated with ASD in CdLS, FXS and Cri du Chat syndromes and trajectory of behaviours and abilities. Cochran *et al.* found no significant changes between time 1 and time 2 in the severity of ASD characteristics in the CdLS and Cri du Chat groups. The FXS group however, were found to show significantly fewer repetitive behaviours and less severe impairments in social interaction at time 2. Taylor

et al. (2011) have also investigated the longer-term course of self-injurious behaviour in individuals with an ID. Their findings indicated that 84% of the sample continued to engage in self-injury after a follow-up of twenty years. In addition, Rice *et al.* (2015) have found a significant decline in physical aggression and temper tantrums with age in people with DS, FXS and William syndrome before 19 years old, while in PWS this decline occurred after 19 years of age. Other longitudinal research has found that low mood, interest and pleasure appears to be a particular characteristic of older individuals (over the age of 15 years) with CdLS (Nelson *et al.*, 2014). This indicates that behavioural phenotypes are not always static and may be related to age. An understanding of how the trajectory of behaviours differs over time can support the identification of individuals who may be at greater risk of particular psychological difficulties. Therefore, results of this kind are fundamental in being able to tailor treatment and intervention for individuals with genetic syndromes and ID.

Follow-up

As cited within the review of the literature detailed above, Sheth *et al*. (2015) conducted an in-depth study describing the clinically significant behaviour in participants with Sotos syndrome. Parents and carers of 38 individuals with Sotos syndrome were recruited who completed questionnaires assessing adaptive behaviour and ability, hyperactivity and impulsivity, repetitive behaviour, autism spectrum phenomenology, self-injury and challenging behaviour, and mood, interest and pleasure. The following study represents a follow-up of the research conducted by Sheth *et al*.

Rationale and Aims

To conclude, although research has investigated the behavioural and psychological characteristics of Sotos syndrome, many of these are still not well defined and little is known about temporal development for people with Sotos syndrome. Developing this knowledge would benefit individuals with Sotos, their family members and professionals working in the field, contributing to a more thorough understanding of associated characteristics to develop and provide the most appropriate services and treatments.

The first aim of this research was to investigate changes over time, via a follow-up study of people with Sotos syndrome who took part in the paper by Sheth *et al*. (2015), in clinically relevant behavioural variables including:

- Adaptive behaviour and ability;
- Hyperactivity and impulsivity;
- Repetitive behaviour;
- ASD, communication and social interaction;
- Challenging behaviour;
- Mood.

Adaptive behaviour was also characterised in greater depth for the participants in the study, with a more detailed measure, with better-established reliability and validity, than initially undertaken at the first time point by Sheth *et al.* (2015).

A second aim was to investigate anxiety in Sotos syndrome following frequent anecdotal reports from parents/carers and limited research evidence about difficulties within this area.

2.3 Methods

Ethical Approval

Ethical review and approval had been obtained by the affiliated research centre as part of the programme of studies of which this was a part (see Appendix E and F).

Design

The study had longitudinal and cross-sectional aspects. To investigate the changes in people with Sotos syndrome as they grow older, a repeated measures design was utilised. Dependent variables were behavioural/psychological measures collected in relation to a group of people with Sotos syndrome, with most measures completed at two-time points: time 1 (T1) and time 2 (T2), approximately seven years apart. Measures were of adaptive behaviour and ability, hyperactivity and impulsivity, repetitive behaviour, communication and social interaction, challenging behaviour and mood.

A number of measures (primarily of anxiety and mood difficulties) were collected only at T2, for the purpose of characterising these areas of possible difficulty for the first time. Data from these measures were compared with published normative data and data collected in relation to other genetic conditions where possible, to contextualise results.

Recruitment

Participants were recruited from a database[10] of those who had completed a previous study in 2010-2011 (data reported by Sheth *et al.*, 2015) and had consented to be re-contacted for future research. This initial sample comprised 38 parents and carers of individuals who had been clinically or genetically diagnosed with Sotos syndrome by a clinical geneticist or a paediatrician. These participants had been recruited from three sources: The Child Growth Foundation and two Clinical Genetics Departments within the UK[11] (Sheth *et al.*, 2015). Of the 38 participants who had completed the previous study, two participants were now deceased and therefore 36 people were contacted. An initial power calculation was not calculated in light of the study being a follow-up and in considering the difficulties of power in the study of rare syndrome groups. The decision was made to consider retrospective power analysis following data collection.

Procedure

Parents and carers of participants who had completed the previous study were sent a letter inviting them to take part in the follow-up study. This letter provided study information and details of an online survey (see Appendix G). The online survey included additional information (see Appendix H), consent forms based on participant age and capacity to consent (see Appendix I1, I2, I3) and a series of questionnaires. Where necessary, parents also consented to be consultees on behalf of the participant. Parents and carers were invited to complete the online survey at a time of their choosing. The survey was open for recruitment for approximately eight months to maximise opportunity for completion. The invitation letter was sent out again approximately five months after initial recruitment to improve return rate. After participants had completed the online survey, they were contacted via email and telephone to thank them for taking part and to organise an additional telephone interview to complete the study. Telephone interviews were organised at the convenience of parents and carers and lasted approximately ninety minutes to two hours. Participants were given the choice to complete this stage all in one go, or over a series of phone calls.

[10] Database held at the affiliated research centre.
[11] These have not been named to maintain anonymity.

Participants

Participants comprised 15 individuals with Sotos syndrome whose parents/caregivers responded to the invitation to take part; this represented a 41.7% return rate of those invited to take part and 39.7% of the total sample size recruited in 2010-2011. The age range of the individuals with Sotos syndrome was 13 - 37 years and the mean 21.9 years (SD = 7.4 years). Nine (60%) of the sample were male and six (40%) were female. The sample had been diagnosed by a combination of paediatricians (33.3%) and clinical geneticists (67.7%). Of the parents/caregivers who responded on behalf of the participants, thirteen were mothers (86.7%) and two were fathers (13.3%). Manual checks indicated that the same parent completed the assessment at both T1 and T2.

Measures

Data from a variety of questionnaires are reported in this study. The majority of these had also been completed at time point 1, while additional measures were also employed.

Repeated Measures

The online survey included eight questionnaires that had been completed with participants in 2010-2011.

The Demographic Questionnaire

The demographic questionnaire provided information on date of birth, gender, diagnosis, as well as a broad measure of mobility and verbal ability (see Appendix J).

The Wessex Scale

The Wessex Scale (Kushlick *et al.,* 1973) is designed to measure ability and level of adaptive behaviour in children and adults with ID (see Appendix K). The measure comprises four subscales including: continence, mobility, self-help skills, speech and literacy to evaluate physical and social abilities of individuals. The questionnaire also offers basic information relating to vision and hearing impairments. Respondents are directed to use Likert scales to indicate how each item refers to the person they care for.

The scale has good inter-rater reliability at item and subscale level for both children and adults (Kushlick *et al.,* 1973).

The Activity Questionnaire

The Activity Questionnaire (TAQ; Burbidge & Oliver, 2008; Burbidge *et al.,* 2010) is an 18-item questionnaire used to measure behaviours associated with hyperactivity, overactivity and impulsivity in people with ID (see Appendix L). The items form three subscales of overactivity, impulsivity and impulsive speech. Parents and carers are directed to use a five-point Likert scale to indicate frequency of each behaviour in the person who they care for, ranging from 'never/almost never' to 'always/almost all the time'. Higher scores are indicative of higher levels of hyperactivity and impulsivity. The measure has been found to be reliable and has good internal consistency (Burbidge *et al.,* 2010).

The Repetitive Behaviour Questionnaire

The Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver, 2008; Moss *et al.*, 2009) is designed to assess repetitive behaviours in children and adults with ID (see Appendix M). The questionnaire asks about 19 different behaviours which comprise five subscales: stereotyped behaviour, compulsive behaviour, insistence on sameness, restricted preferences and repetitive speech. Respondents are asked to think about how frequently the person they care for has displayed each behaviour over the last month and are asked to select a response on a five-point Likert scale, ranging from 'never' to 'more than once a day'. Higher scores are indicative of greater levels of repetitive behaviours. Examination of the RBQ has demonstrated good psychometric properties (Moss *et al.,* 2009).

Social Communication Questionnaire – Current Version

The Social Communication Questionnaire (SCQ; Rutter *et al.*, 2003) is a 40-item screening questionnaire and is used to assess characteristics/behaviours associated with ASD (see Appendix N). Each item can be answered 'yes' or 'no' which corresponds to

the presence (score of 1) and absence (score of 0) of autistic characteristics and impairments. Items are categorised into three subscales: communication, reciprocal social interaction and restricted, repetitive and stereotyped patterns of behaviour. The SCQ also provides clinically relevant classifications with scores of 15 and above indicating an ASD, and scores of 22 and above indicating Autism. High scores are therefore indicative of greater impairment in social communication. It can be used to evaluate those aged over 4 years and whose mental age exceeds 2 years. The measure can be completed by a parent and carer. It is widely employed clinically and in research, has good psychometric properties and can be analysed at an item level (Berument *et al.*, 1999; Moss *et al.*, 2013). While the Lifetime version of the SCQ was used in 2010-2011 (which focuses on developmental history), the current version was utilised in this study to enable current characteristics to be evaluated.

The Sociability Questionnaire for People with Intellectual Disability

The Sociability Questionnaire for People with Intellectual Disability (SQID; Nelson *et al.*, 2016) is designed to measure sociability in children and adults with ID who have a range of verbal abilities (see Appendix O). The questionnaire comprises 25 items describing various social situations with familiar and unfamiliar people over the previous two-month period. The majority of items direct care givers to select a response on a seven-point Likert scale ranging from 'very shy' to 'very sociable', with four questions asking about frequency of social interaction and there are also four 'yes/no' questions. Higher scores are suggestive of higher levels of sociability, while lower scores are suggestive of lower levels of sociability (and higher levels of shyness) The measure was developed specifically for people with ID and has been found to have good inter-reliability and validity (Nelson *et al.*, 2016).

The Challenging Behaviour Questionnaire

The Challenging Behaviour Questionnaire (CBQ; Hyman *et al.*, 2002) is designed to measure the presence or absence of behaviours in people with ID, including physical and verbal aggression, self-injury, destruction of property and inappropriate vocalisations, over the most recent month (see Appendix P). The questionnaire includes

eight items relating to the occurrence, the frequency and intensity of different behaviours. The CBQ has been found to be a reliable measure with good psychometric properties (Hyman *et al.*, 2002).

The Mood Interest and Pleasure Questionnaire – Short Version

The Mood Interest and Pleasure Questionnaire – Short Version (MIPQ-S; Ross & Oliver, 2003; Ross *et al.*, 2008) is a questionnaire designed to assess mood, interest and pleasure in people with ID (see Appendix Q). The questionnaire includes 12 items and asks respondents to rate each item using Likert scales that describe different frequency levels. The items form two subscales, 'Mood' and 'Interest and Pleasure'. A choice of responses are offered on a five-point Likert scale and parents/caregivers are directed to consider how the person they care for has presented over the most recent two weeks. Higher scores indicate more positive mood levels and higher levels of interest and pleasure. The questionnaire has been found to have good internal consistency and reliability (Ross & Oliver, 2003).

Parent/Caregiver Measure

A measure was also included on the online survey to investigate anxiety and depression in parents and carers themselves. This had been completed as part of the study in 2010-2011.

The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) measures symptoms of depression and anxiety (see Appendix V). It includes 14 items, each with a choice of four responses which rate the amount of time an individual has experienced each statement in the recent week. Higher scores on the HADS indicate that the individual is experiencing more symptoms of anxiety and depression. The HADS has been found to be a valid and reliable measure (Bjelland *et al.*, 2002).

Additional Measures

To continue collecting data on the behavioural and psychological characteristics of Sotos syndrome an additional measure was incorporated into the online survey. Additional measures were also carried out during telephone interviews. This supported the exploration of ASD phenomenology and adaptive behaviour in more detail, in addition to anxiety.

Sensory Experiences Questionnaire – short form

The Sensory Experiences Questionnaire short form (SEQ; Baranek *et al.*, 2006) captures information relating to an individual's sensory experience and how they use their senses (see Appendix R). The short form of the questionnaire comprises six questions about sound, seven about sight, eight about touch, four about taste/smell and five questions about movement. Eight additional items also ask about the frequency of obsessive behaviours around senses and food preferences. Items relate to three patterns; hyporesponsive, hyperresponsive and sensory seeking, within two contexts: social and non-social. Hyporesponsiveness is defined by the authors as a lack of orienting and reacting to sensory stimuli, and hyperresponsiveness is defined as behavioural over-reactivity to sensory stimuli. The SEQ explores whether sensory features/experiences occur more often in social contexts which are defined as situations with people, e.g. tolerating physical contact with people, and non-social contexts with a focus on environmental settings, e.g. responding to loud sounds or textured objects (Baranek *et al.*, 2006). Higher scores for each pattern/subscale indicate greater frequency and intensity of sensory features. The measure was designed for use with children with Autism and developmental disabilities. It has also been used to characterise sensory patterns in genetic syndromes (Walz & Baranek, 2006). Baranek *et al.* (2006) have found good internal consistency, test-retest reliability and validity.

The Anxiety, Depression and Mood Scale

Anxiety, Depression and Mood Scale (ADAMS; Esbensen *et al.*, 2003) is a brief measure of anxiety and mood (see Appendix S). The measure comprises 28 items which describe different behaviours. It asks respondents to describe how much the person they care for has presented with the listed behaviours over the most recent six

months using a four-level rating scale: 'behaviour has not occurred, or is not a problem', 'behaviour occurs occasionally, or is a mild problem', 'behaviour occurs quite often, or is a moderate problem' and 'behaviour occurs a lot, or is a severe problem'. Items comprise of five subscales: manic and hyperactive, depressed mood, social avoidance, general anxiety and obsessive-compulsive behaviour. Higher scores indicate higher levels of anxiety and mood difficulties. The measure has been designed for use with individuals with an ID and has been found to be a reliable and valid measure (Esbensen *et al.*, 2003).

The Spence Children's Anxiety Scale – Parent Version

The Spence Children's Anxiety Scale – Parent Version (SCAS-P; Spence, 2000) is also a brief measure of anxiety (see Appendix T). The measure consists of 38 items describing anxiety which asks respondents to use a four-level rating scale 'never', 'sometimes', 'often', 'always' to rate how often each feeling/thought/behaviour occurs in their child/person they care for and to provide an overall measure of anxiety. The items on the SCAS-P can be divided up into six subscales: separation anxiety, generalised anxiety, social phobia, panic attack and agoraphobia, physical injury fears and obsessive compulsive. There is also one open-ended question regarding anxiety (unscored) which aims to elicit any other sources of anxiety for the individual. Higher scores indicate higher levels of anxiety and worry. The SCAS-P has been found to have relatively good psychometric properties and has been useful for research purposes (Nauta *et al.*, 2004). The SCAS-P was originally developed for use with children, but has also been used in research with people of a variety of ages with other genetic syndromes associated with ID (Crawford *et al.*, 2017).

The Vineland Adaptive Behavior Scales

The Vineland Adaptive Behavior Scales survey version (VABS; Sparrow *et al.*, 2005) is a widely used measure of level of ability and daily adaptive functioning (see Appendix U) and is administered as a semi-structured interview. The VABS offers summary scores for communication, daily living, social and motor skills through ratings of 'usually', 'sometimes or partially' and 'never' on the performance of a variety of different day to day activities. Ratings allow age equivalent and standard scores to be

calculated, indicating level of ability. The instrument has been found to be a reliable and valid measure (Sparrow *et al*., 2005). The VABS provides more in-depth information than the Wessex Scale and was administered to provide additional detail about participant's abilities and day to day functioning and to demonstrate a better characterisation of adaptive ability. Although, the VABS is not specifically designed for use with people with ID, it has often been used in research with individuals with genetic syndromes associated with ID to investigate adaptive behaviour (e.g. Di Nuovo & Buono, 2011).

The VABS, ADAMS and SCAS-P measures were completed over the telephone.

Data analysis

Repeated measures data

Data were analysed using non-parametric tests due to the small sample size (Field, 2013). Wilcoxon Signed-Ranks tests were utilised to assess overall group changes in subscale and total questionnaire scores from T1 to T2. This was carried out for the TAQ, RBQ, SCQ, SQID and MIPQ-S, to identify whether there were any changes over time for the group as a whole in impulsivity and overactivity, repetitive behaviours, social communication and ASD characteristics, sociability and mood. This was also performed in relation to parent/caregiver scores on the HADS to identify changes in anxiety and affect. Findings from these analyses are displayed in Tables 16, 17, 19, 20 and 23. Effect sizes for changes over time, *r*, are reported using guidelines for non-parametric tests from Fritz *et al.* (2012), and considered in relation to Cohen's (1988) guidelines (0.1 small, 0.3 medium, 0.5 large). Spearman's rank order correlations were also reported for subscales and total scores to establish correlational relationships between scores at T1 and T2. Alpha level was set at 0.05, despite multiple comparisons, since the small sample increases the risk of type 2 errors (incorrectly accepting the null hypothesis) which may lead to overlooking clinically important information. However, it is acknowledged throughout that replication of results will be all the more crucial as a result, due to risk of type 1 errors (incorrectly rejecting the null hypothesis). Categorical data, such as proportions of participants showing challenging behaviours as measured by the CBQ and proportions of participants meeting clinically-relevant criteria on certain measures (e.g., meeting criteria indicative of ASD on the SCQ), were analysed using McNemar tests to evaluate differences between T1 and T2.

The formation of radar charts at T1 and T2 aided visualisation of the nature of repetitive behaviours, in the form of item level scores on the RBQ.

Single timepoint data

Mean scores on the SEQ were compared with available normative and comparative data collected by Baranek (2006) (medians were not available for this set of comparison data). Characterisation of anxiety was derived from scores on the ADAMS and the SCAS-P. Mean and median scores were compared with published normative data and with comparative data from a study (Crawford *et al.*, 2017) of individuals with FXS (N=19, mean age=24.19), CdLS (N=13, mean age=18.75) and RTS (N=27, mean age=23.55), for which the study authors were kindly able to provide data.

Kruskal-Wallis analyses were used to assess differences between the groups in anxiety scores, with post hoc Mann-Whitney Tests where relevant.

One sample Wilcoxon Signed-Rank Tests were performed to investigate whether there were differences between the Sotos group and normative medians for the SCAS-P and ADAMS.

2.4 Results

Demographic Characteristics

Demographic data for the participant sample for T1 and T2 are presented in Table 14. A Mann-Whitney U Test revealed no significant differences in age and questionnaire subscale/total scores between those who participated in the follow-up and those who did not.

Table 14. Demographic characteristics from T1 and T2

		T1[12]	T2
N		15	15
Age (years)	***M***	15.5	21.9
	(SD)	(7.5)	(7.4)
	Range	7-31	13-37
Gender	**N (%) male**	9 (60)	9 (60)
	N (%) female	6 (40)	6 (40)
Residence	**% living at home**	80	73.3
	% living in supported living/residential home	20	26.6
Self-help[13]	**% Partly able/able[14]**	93.3	93.3
Mobility[13]	**% Mobile[15]**	93.3	86.7
Vision[13]	**% Normal**	86.7	86.7
Hearing[13]	**% Normal**	73.3	66.7
Speech[13]	**% Verbal/partly verbal**	100	100

Adaptive Behaviour

Scores on the Wessex scale indicated that the majority of participants at T2 were partly able/able and mobile, while all participants were described as verbal/partly verbal (see Table 14). The VABS was completed at T2 to provide a more in-depth characterisation of the level of ability and adaptive behaviour of participants. Mean subdomain scale scores, age equivalent scores and domain standard scores are displayed in Table 15. Individual participant scores were quite variable indicating a diverse picture of relative strengths and areas of difficulty, while the mean domain standard scores and adaptive behaviour composite were illustrative of developmental delay and low functioning. Mean subdomain scale scores were in the low range for receptive, expressive, written, personal, domestic, community and fine motor skills areas, while they were in the moderately low range for play and leisure, coping skills and gross motor skills. Mean domain standard scores were all in the low range. Anecdotally, many parents commented that skills in adaptive functioning often required a lot of repetitive teaching and prompting. No significant correlations were found between the adaptive behaviour composite and total scores of the other measures collected as part of this study.

[12] T1 data refers to the sample of 15 participants who took part in the follow-up from the sample collected by Sheth *et al.* (2015).
[13] Data derived from Wessex Scale (Kushlick *et al.*, 1973).
[14] Those scoring six or above on total score of the self-help subscale (items g-i).
[15] Those scoring six on total score of the mobility subscale (items e & f).

Table 15. Mean and standard deviation domain and subdomain scores on the VABS at T2.

VABS Subdomain/domain	**Subdomain Scores**		**Domain Standard Scores (population mean 100, SD 15)**
	Scale Scores (population mean 15, SD 3)	**Age Equivalent Scores (years)**	
Receptive	7.07 (3.00)	4.88 (2.76)	
Expressive	7.47 (3.54)	6.07 (2.97)	
Written	8.13 (2.90)	8.10 (3.11)	
Domain: Communication			**47.80 (20.69)**
Personal	5.93 (3.43)	7.33 (4.42)	
Domestic	6.67 (3.37)	7.97 (5.32)	
Community	6.67 (2.94)	8.57 (4.05)	
Domain: Daily Living Skills			**51.13 (14.91)**
Interpersonal relationships	6.93 (3.67)	5.98 (3.92)	
Play and leisure time	10.13 (4.12)	10.49 (6.58)	
Coping skills	9.47 (3.70)	8.37 (5.51)	
Domain: Socialization			**60.93 (17.21)**
Gross motor skills	9.13 (3.18)	3.99 (5.06)	
Fine motor skills	8.60 (5.33)	8.22 (7.25)	
Domain: Motor Skills			**60.93 (19.80)**
Adaptive Behaviour Composite			**51.93 (15.31)**

Impulsivity and Overactivity

Statistically significant differences were found on all subscale scores and the total score on the TAQ between T1 and T2 (see Table 16). This indicates that hyperactivity and impulsivity reduced over time.

Table 16. TAQ subscale and total scores from T1 and T2.

Subscale		**T1**	**T2**	**Wilcoxon Signed Rank Test**	**Effect size (*r*)**
Impulsivity	*M* (SD)	14.45 (7.58)	10.40 (8.45)	Z = -2.04	0.37
	Med (IQR)	16.00 (13.00)	9.00 (13.00)	p = .041*	
Overactivity	*M* (SD)	9.43 (10.04)	5.93 (9.73)	Z = -2.40	0.44
	Med (IQR)	7.00 (15.75)	1.00 (11.00)	p = .016*	
Impulsive speech	*M* (SD)	5.71 (4.38)	3.64 (3.91)	Z = -2.02	0.37
	Med (IQR)	5.00 (8.75)	2.00 (5.25)	p = .043*	
Total	*M* (SD)	29.21 (20.40)	19.73 (20.32)	Z = -2.73	0.50
	Med (IQR)	23.00 (35.00)	17.00 (25.00)	p = .006*	

Repetitive Behaviours

A Wilcoxon Signed-Ranks Test indicated no significant differences between the two timepoints in subscale scores or total scores on the RBQ (see Table 17), indicating no strong evidence of change over time in relation to repetitive behaviours.

Table 17. RBQ subscale and total scores from T1 and T2.

Subscale		**T1**	**T2**	**Wilcoxon Signed Rank Test**	**Effect size (*r*)**
Stereotyped behaviour	*M* (SD) *Med* (IQR)	2.73 (3.01) 2.00 (4.00)	3.07 (3.83) 2.00 (7.00)	*Z* = -.54 *p* = .592	0.10
Compulsive behaviour	*M* (SD) *Med* (IQR)	5.07 (5.47) 3.00 (9.25)	4.20 (6.19) 2.00 (6.00)	*Z* = -.67 *p* = .504	0.12
Insistence on sameness	*M* (SD) *Med* (IQR)	2.86 (2.35) 2.50 (3.25)	3.33 (2.92) 3.00 (4.00)	*Z* = -1.04 *p* = .296	0.19
Restricted preferences	*M* (SD) *Med* (IQR)	4.36 (3.77) 4.00 (6.50)	3.87 (3.54) 3.00 (2.00)	*Z* = -.98 *p* = .325	0.18
Repetitive speech	*M* (SD) *Med* (IQR)	5.38 (4.09) 4.00 (7.00)	4.47 (3.72) 3.00 (5.00)	*Z* = -.42 *p* = .674	0.08
Total	*M* (SD) *Med* (IQR)	20.46 (16.80) 14.00 (29.00)	18.93 (17.38) 13.00 (18.00)	*Z* = -.15 *p* = .878	0.03

Figure 4 illustrates that the distinctive repetitive behaviour profile noted by Sheth *et al.* (2015) at T1 is broadly replicated at T2 with spikes remaining in repetitive questioning and preference for routine. During administration of other measures, for example the ADAMS, parents frequently anecdotally reported that their children asked repetitive questions while anxious. The profile depicts a possible increase in body stereotypy and insistence on things being 'just right', and a decrease in hoarding behaviours and repetitive phrases, although none of these changes were statistically significant in item level analysis.

Figure 4. Radar charts illustrating the mean scores for each item/question on the Repetitive Behaviour Questionnaire at T1 and T2 (see Appendix M)

Communication, Social Interaction and Autism Spectrum Disorder

Parental report indicated that three participants had existing diagnoses of ASD. A proportion of participants also scored above the clinical cut-off for ASD (53.33%) on the SCQ. Table 18 shows a comparison of these proportions between T1 and T2 and although no statistically significant changes were found using McNemar tests, this illustrates that fewer participants met the cut-off scores for ASD and Autism at T2.

Table 18. Proportions of participants meeting ASD and Autism cut-off scores on the SCQ.

		T1	T2
ASD cut-off	*N*	12/15	8/15
	%	80	53.33
Autism cut-off	*N*	6/15	4/15
	%	40	26.67

A Wilcoxon Signed-Rank test indicated that T2 total scores and reciprocal social interaction subscale scores were statistically lower than at T1 (see Table 19). A reduction in scores is indicative of fewer ASD-related behaviours. It should be noted that the 'lifetime' version of the SCQ, with some questions assessing behaviour at age 4-5 years, had been used at T1, whilst the 'current' version was used at T2. However, there is a precedent for comparing the two versions of the SCQ by Richards *et al.* (2016).

Table 19. SCQ subscale and total scores from T1 and T2.

Subscale		**T1**	**T2**	**Wilcoxon Signed Rank Test**	**Effect size (*r*)**
Communication	*M* (SD)	7.77 (3.14)	7.33 (1.92)	*Z* = -.27	0.05
	Med (IQR)	8.00 (4.00)	7.00 (3.00)	*p* = .788	
Restricted, repetitive and stereotyped behaviour	*M* (SD)	3.40 (2.47)	2.53 (2.56)	*Z* = -1.50	0.27
	Med (IQR)	3.00 (5.00)	1.00 (8.00)	*p* = .133	
Reciprocal social interaction	*M* (SD)	7.88 (4.26)	6.13 (3.80)	*Z* = -2.37	0.43
	Med (IQR)	9.00 (7.00)	7.00 (7.00)	*p* = .018*	
Total	*M* (SD)	19.99 (8.97)	16.73 (6.24)	*Z* = -2.02	0.37
	Med (IQR)	20.43 (12.79)	16.00 (11.00)	*p* = .044*	

Table 20 displays mean and median scores on the familiar and unfamiliar subscales of the SQID. Wilcoxon Signed-Ranks Tests did not find a statistically significant difference between T1 and T2 scores.

Table 20. SQID subscale scores from T1 and T2.

Subscale		**T1**	**T2**	**Wilcoxon Signed Rank Test**	**Effect size (*r*)**
Total Unfamiliar	*M* (SD) *Med* (IQR)	29.67 (14.18) 32.00 (26.00)	28.67 (16.38) 26.00 (33.00)	*Z* = -.46 *p* = .649	0.08
Total Familiar	*M* (SD) *Med* (IQR)	43.33 (10.81) 44.00 (13.00)	42.87 (12.16) 48.00 (22.00)	*Z* = -.35 *p* = .729	0.06

Table 21 shows the descriptive statistics on the SEQ (collected only at T2). Higher scores indicate greater frequency and intensity of atypical sensory features. Scores were compared against normative data (of typically developing children) and data from groups with ASD and developmental disabilities, as well as cut-off criteria (Baranek 2006). This data had been collected as part of a sensory experiences project where participants were aged between 1-8 years. At a group level, scores appeared to offer a variable picture of sensory experiences. Scores were lower than typically developing controls for sensory seeking, non-social contexts and total score, while they were higher than controls for hyperresponsiveness, hyporesponsiveness and social contexts.

Table 21. Comparison of mean scores on the SEQ between Sotos group and Norms (medians for norms not available).

Subscale	**Sotos syndrome N=15**	**Typically developing children N = 53**	**ASD children N= 75**	**Developmental disabilities children N = 44**
Sensory seeking *M* (SD)	21.53 (11.64)	29.74 (8.68)	36.21 (8.39)	30.59 (9.20)
Hyperresponsiveness *M* (SD)	26.27 (14.27)	24.08 (4.62)	35.28 (7.14)	28.50 (6.10)
Hyporesponsiveness *M* (SD)	12.00 (5.14)	8.68 (1.91)	13.51 (4.34)	10.45 (3.25)
Social *M* (SD)	18.87 (9.01)	15.92 (2.85)	23.24 (4.62)	17.82 (4.53)
Nonsocial *M* (SD)	39.33 (18.59)	45.49 (10.15)	59.70 (11.02)	50.30 (10.67)
Total *M* (SD)	59.80 (27.06)	62.49 (11.50)	85.00 (14.09)	69.55 (12.72)

The proportion of participants reaching cut-off scores was also investigated using criteria set out by Baranek (2006). These criteria outline typical and atypical sensory patterns. The area with the highest proportion of participants reaching the 'deficient' range (representing scores more than 2 standard deviations below the mean), and therefore showing atypically high levels, was hyporesponsiveness, which is defined as a lack of orienting/reacting to sensory stimuli (see Table 22).

Table 22. Proportions of participants reaching cut-off scores on the SEQ.

Subscale		**Cut-offs for 'Typical' Range**	**Cut-offs for 'At Risk' range**	**Cut-offs for 'Deficient' range**
Sensory seeking	*N*	14/15	0/15	1/15
	%	93.33	0	6.67
Hyperresponsiveness	*N*	12/15	0/15	3/15
	%	80	0	20
Hyporesponsiveness	*N*	8/15	1/15	6/15
	%	53.33	6.67	40
Social	*N*	10/15	2/15	3/15
	%	66.67	13.33	20
Nonsocial	*N*	13/15	1/15	1/15
	%	86.67	6.67	6.67
Total	*N*	12/15	0/15	3/15
	%	80	0	20

The relationship between total scores on the SEQ and the SCQ was investigated using Spearman's Rank Order Correlation. There was a positive correlation between the two variables (r_s = .55, n = 15, p = .034) indicating that individuals with higher total scores on the SEQ also generally displayed higher scores on the SCQ.

Challenging Behaviour

There were some indications of possible reductions over time in the frequency with which participants were reported to have shown challenging behaviours in the month prior to assessment, although none of these reached statistical significance. In relation to individual items on the CBQ, 4/15 (26.7%) participants displayed self-injurious behaviours at T2, compared to 5/15 (33.3%) at T1. The most common self-injurious behaviour at T1 was hitting self with body (N=4) and biting self (N=3), while at T2 it

was biting self (N=3) and scratching self (N=3). Only one participant who had not shown self-injury at T1 was noted to have shown self-injury at T2. In addition, 3/15 (20%) participants showed physical aggression at T2, compared to 7/15 (46.7%) at T1, and 3/15 (20%) participants showed destruction of property compared to 5/15 (40%) at T1. No participant who had not displayed physical aggression or destruction of property at T1 subsequently showed this at T2. Stereotyped behaviour was the only category of behaviour displayed more commonly at T2: 6/15 had shown stereotyped behaviour compared to 4/15 (26.7%) at T1.

Mood, Interest and Pleasure

Descriptive statistics for the mood and interest and pleasure subscales and total score of the MIPQ-S are displayed in Table 23. A Wilcoxon Signed-Ranks Test indicated no significant differences between the scores on the subscales and total score between T1 and T2, suggesting no significant changes in these scores over time.

Table 23. MIPQ-S subscale and total scores from T1 and T2

Subscale		**T1**	**T2**	**Wilcoxon Signed Rank Test**	**Effect size (*r*)**
Mood	*M* (SD)	21.04 (2.71)	21.73 (2.79)	*Z* = -1.29	0.23
	Med (IQR)	22.00 (5.00)	23.00 (1.00)	*p* = .198	
Interest and Pleasure	*M* (SD)	16.87 (3.18)	17.73 (3.17)	*Z* = -.87	0.16
	Med (IQR)	18.00 (4.00)	17.00 (4.00)	*p* = .384	
Total	*M* (SD)	37.90 (4.83)	39.47 (5.36)	*Z* = -1.34	0.25
	Med (IQR)	39.00 (9.00)	41.00 (4.00)	*p* = .180	

Correlational Analysis

The relationship between the scores on all the above measures between T1 and T2 was also investigated using Spearman's Rank Order Correlations. Significant correlations were found between scores at T1 and T2 for all subscale and total scores suggesting that, overall, individuals who scored higher at T1 also scored higher at T2.

Anxiety

To characterise anxiety in more detail, scores on the SCAS-P and the ADAMS were analysed (data only collected at T2). Higher scores on these two measures is indicative of more symptoms of anxiety, worry and mood related difficulties.

For the SCAS-P, a number of sources of comparison data were used. Nauta *et al.* (2004) provide comparison data for a group of children who had been given a diagnosis of anxiety disorder (N=484) and a group of normal controls (N=261) who had been recruited from two sites in Australia and one in the Netherlands, aged 6-18 years old. Mean subscale and total scores for Nauta *et al.*'s samples, alongside those for the current sample, are displayed in Table 24. All mean scores for the Sotos syndrome group are higher than those for the 'normal' sample. Whilst some scores for the Sotos group are lower than for samples of children with diagnoses of anxiety, it is notable that scores on the obsessive-compulsive subscale were higher than the anxiety controls which suggests this may be a particular area of difficulty for people with Sotos syndrome.

Median scores for a typically developing child sample were derived from the Spence Children's Anxiety Scale Website (https://www.scaswebsite.com/index.php?p=1_69) where percentile data were offered for boys and girls aged 10-13 years. This allowed one sample Wilcoxon Signed-Rank Tests to be performed to compare the Sotos syndrome group in this sample with the median scores for the normal controls. Where the median scores provided by the authors differed for boys and girls, the higher score was taken, to provide a more conservative test. The null hypothesis of no difference in median scores from the normative sample could be rejected for panic attack and agoraphobia ($Z = 2.81$, $p = .005$, $r = 0.53$), obsessive-compulsive behaviour ($Z = 3.19$, $p = .001$, $r = 0.60$) and the total score ($Z = 2.01$, $p = .044$, $r = 0.38$), with the Sotos group scoring significantly higher than the comparison group in these areas (see Figure 5).

Table 24. Comparison of SCAS-P scores between Sotos group and control groups. (median scores not available for groups of anxiety and normal controls)

Subscale		**Anxiety Controls N=484**	**Sotos Syndrome N=15**	**Normal Controls N=261**
Separation Anxiety	*M* (SD) *Med* (IQR)	6.9 (4.1)	4.0 (3.4) 3.0 (6.3)	2.6 (2.8)
Generalised Anxiety	*M* (SD) *Med* (IQR)	6.6 (3.1)	4.6 (3.8) 3.0 (5.5)	2.7 (2.0)
Social Phobia	*M* (SD) *Med* (IQR)	7.7 (3.8)	5.6 (4.3) 4.5 (4.5)	4.2 (2.8)
Panic attack and agoraphobia	*M* (SD) *Med* (IQR)	3.6 (3.9)	3.5 (3.8) 2.5 (7.0)	1.0 (1.6)
Physical injury fears	*M* (SD) *Med* (IQR)	4.1 (2.8)	3.7 (2.7) 4.0 (4.3)	2.6 (2.3)
Obsessive compulsive	*M* (SD) *Med* (IQR)	3.0 (3.1)	4.1 (4.5) 2.5 (4.8)	1.1 (1.7)
Total	*M* (SD) *Med* (IQR)	31.8 (14.1)	25.6 (19.2) 20.0 (36.5)	14.2 (9.7)

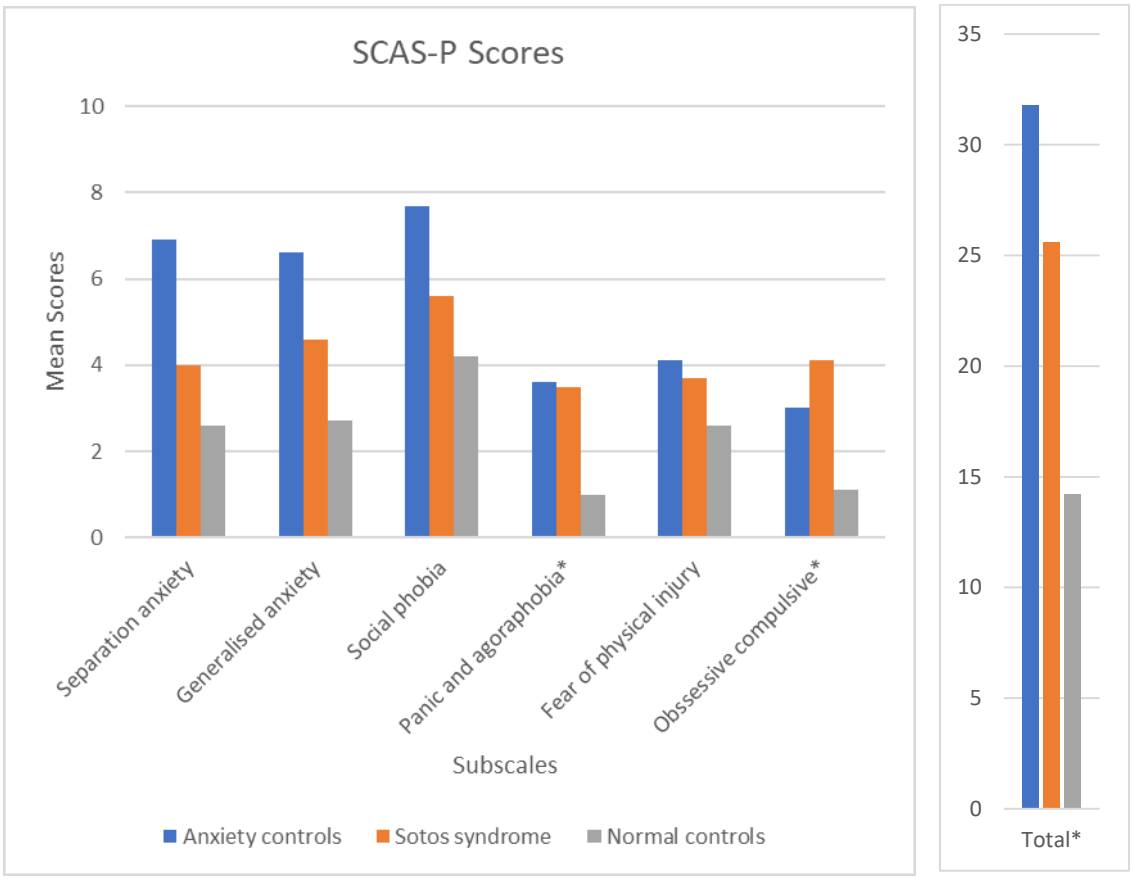

Figure 5. Chart illustrating comparisons of the mean SCAS-P scores in Sotos group with anxiety and norm data.

Subscale and total scores of the SCAS-P were also compared to samples of participants with FXS, CdLS and RTS syndromes from data collected and provided for the current analysis by the first author of Crawford *et al.* (2017). Participants in this study had been recruited from syndrome support groups and as part of ongoing research. A Kruskal-Wallis analysis identified a significant difference in generalised anxiety, separation anxiety, social phobia and total scores across syndrome groups (see Table 25).

The total SCAS-P score was higher than scores for the FXS and RTS groups, and lower only than the score for the CdLS group, a group noted for high levels of anxiety (e.g. Basile *et al.*, 2007; Kline *et al.*, 2007).

The Sotos group had higher subscale scores for generalised anxiety, separation anxiety and SCAS-P total than the FXS and RTS syndrome groups, but lower than the CdLS group. Post hoc analyses using Mann-Whitney U Tests illustrated that the Sotos group obtained significantly higher scores for generalised anxiety than the RTS group. For social phobia, inspections suggested that the Sotos group had significantly higher scores

than the other groups, although post hoc analyses found this was only statistically significant when compared to the RTS group. For the obsessive-compulsive subscale, it is notable that the Sotos group had the highest mean score (although the Kruskal-Wallis test didn't indicate significant between-group differences, so post-hoc analysis was not conducted).

Table 25. Comparison of subscale scores of the SCAS-P with results from Kruskal-Wallis Tests and post hoc analyses

		Sotos	**FXS**	**RTS**	**CdLS**	X^2	**df**	***p***	**Post hoc analyses**
N		15	19	27	13				
Mean age		21.93	24.19	23.55	18.75				
Separation anxiety	*M* (SD)	4.00 (3.35)	3.81 (3.55)	3.01 (2.49)	6.57 (3.00)	9.89	3	.020*	CdLS>FXS, RTS
	Med (IQR)	3.00 (6.25)	2.00 (6.50)	2.40 (3.80)	7.00 (4.50)				
Generalised anxiety	*M* (SD)	4.64 (3.84)	3.11 (2.87)	2.75 (2.72)	5.31 (3.17)	9.99	3	.019*	CdLS>FXS, RTS
	Med (IQR)	3.00 (5.50)	2.00 (5.00)	2.00 (3.00)	5.00 (4.50)				**Sotos>RTS**
Social phobia	*M* (SD)	5.57 (4.27)	3.70 (4.08)	1.67 (2.14)	3.27 (2.77)	13.68	3	.003*	**Sotos>RTS**
	Med (IQR)	4.50 (4.50)	2.00 (6.00)	1.00 (3.00)	3.00 (5.00)				
Panic attack and agoraphobia	*M* (SD)	3.50 (3.80)	3.62 (4.42)	2.51 (2.42)	4.56 (3.89)	2.61	3	.455	
	Med (IQR)	2.50 (7.00)	2.00 (5.00	2.00 (3.00)	4.00 (6.50)				
Physical Injury	*M* (SD)	3.71 (2.73)	3.63 (2.85)	2.73 (2.46)	5.00 (2.83)	6.31	3	.097	
	Med (IQR)	4.00 (4.25)	3.00 (5.00)	2.00 (3.00)	4.00 (4.00)				
Obsessive Compulsive	*M* (SD)	4.14 (4.54)	1.84 (2.41)	2.65 (3.03)	2.95 (2.74)	5.30	3	.151	
	Med (IQR)	2.50 (4.75)	1.00 (3.00)	2.00 (4.00)	2.00 (3.00)				
Total	*M* (SD)	25.57 (19.23)	19.71 (16.50)	15.32 (11.05)	27.66 (13.08)	8.57	3	.036*	CdLS>RTS
	Med (IQR)	20.00 (36.50)	11.00 (28.50)	12.00 (14.35)	27.00 (22.38)				

Scores on the ADAMS are displayed in Table 26 and were compared to normal controls which consisted of a group of 323 people with ID without psychiatric diagnoses (Esbensen *et al.*, 2003). One sample Wilcoxon Signed-Rank Tests were performed to compare the Sotos syndrome group in this sample with the median scores for the normal controls of individuals with ID. Median scores were derived from percentile scores detailed in Esbensen *et al.* This led to rejection of the null hypothesis for social avoidance ($Z = 2.08$, $p = .037$, $r = 0.38$) and general anxiety *($Z = 2.22$, $p = .026$, $r = 0.41$)*. Figure 6 also displays these results.

Table 26. Comparison of ADAMS scores between Sotos group and control group.

Subscale		**Sotos Syndrome N=15**	**Normal controls N=323**
Manic and hyperactive	*M* (SD)	5.00 (4.21)	5.29 (3.63)
	Med (IQR)	5.00 (6.50)	5.50 (5.00)
Depressed mood	*M* (SD)	3.93 (4.25)	4.65 (4.10)
	Med (IQR)	1.5 (5.25)	3.00 (6.00)
Social avoidance	*M* (SD)	8.33 (6.34)	4.36 (4.31)
	Med (IQR)	8.00 (11.50)	4.00 (7.00)
General anxiety	*M* (SD)	8.60 (5.01)	6.02 (4.48)
	Med (IQR)	8.50 (8.50)	5.00 (6.75)
Obsessive compulsive behaviour	*M* (SD)	3.80 (3.34)	2.20 (2.60)
	Med (IQR)	2.50 (6.50)	2.00 (5.00)
Total	*M* (SD)	27.79 (17.42)	Not available
	Med (IQR)	23.00 (28.50)	

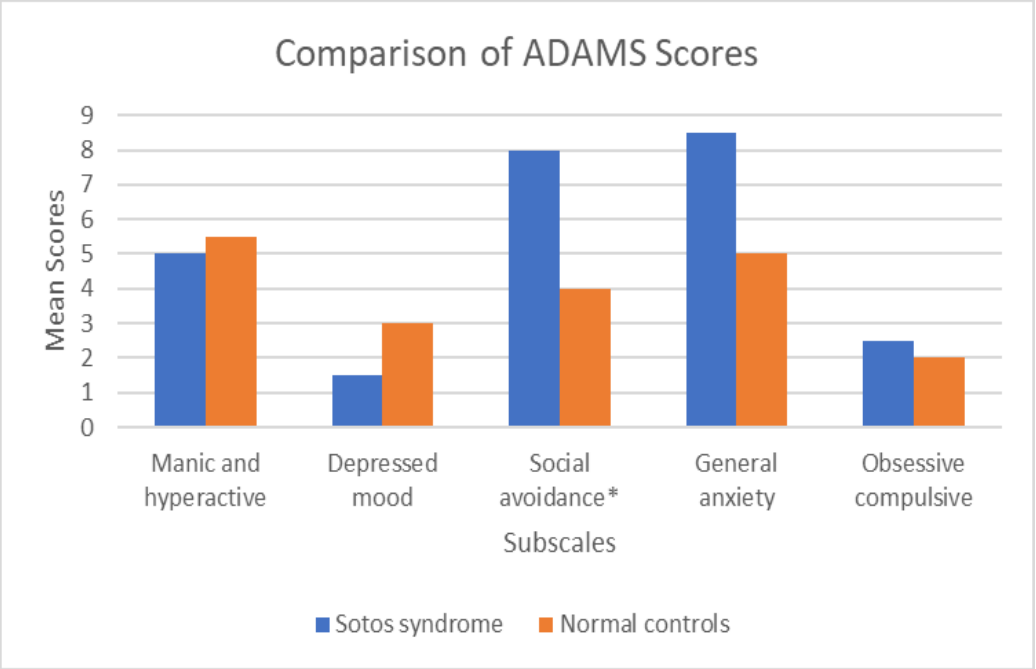

Figure 6. Chart illustrating comparisons of the median ADAMS scores in Sotos group with norm data.

Parent/Caregiver

A significant difference was found between parent/caregiver total scores on the HADS between timepoints using a Wilcoxon Signed-Rank Test (Z = -2.52, p = .012, r = 0.46). Inspection of median scores (6.00 at T1 and 11.00 at T2) indicates an increase in levels of anxiety and depression. Spearman's Rank Order Correlations were also performed to investigate the relationships between parental/caregiver total scores on the HADS with participants' scores on the questionnaires. Significant correlations were found for total scores on the TAQ (r_s = .73, n = 14, p = .003), the SCAS-P (r_s = .59, n = 13, p = .034) and the ADAMS (r_s = .66, n = 13, p = .015).

2.5 Discussion

The current study offers a seven-year follow-up of behavioural and psychological variables, including overactivity, repetitive behaviour, social and communication skills, challenging behaviour and mood, for individuals with Sotos syndrome. It provides, to the author's knowledge, the first longitudinal study of behaviour for this group. In addition, the study characterises possible areas of difficulty with mental health, especially anxiety, which has anecdotally presented as a specific area of difficulty for people with Sotos syndrome and their families.

Parents and carers of individuals with Sotos syndrome who had participated in a previous study were invited to take part and completed a number of standardised questionnaires, the majority of which were designed for use with people with ID, or for which suitable comparison data were available. Fifteen participants were recruited. Reductions over time in impulsivity and overactivity were statistically significant, with medium effect sizes. There was also a decrease in the proportion of individuals reaching scores indicative of ASD and a statistically significant reduction in total scores on the screening measure, and on reported impairments associated with reciprocal social interaction (both with medium effect sizes). This suggests an interesting picture of ASD phenomenology may exist over time. No statistically significant temporal changes were found for other characteristics, indicating possible stability in areas such as repetitive behaviour and mood. Although small N reduces the possibility of detecting significant changes, the effect size of the changes in many of these measures were also

small. Anecdotal reports of anxiety difficulties were corroborated by this research, and characterisation of the profile of anxiety indicated possible peaks in areas including panic, obsessive-compulsive behaviour and social avoidance.

2.5.1 Summary of Main Results

Adaptive Behaviour and Ability

In the current study a more in-depth exploration of ability was undertaken to further characterise day to day functioning within the group. The mean adaptive behaviour composite score was 51.93 which is well below the normative mean score of 100. Developmental delay and intellectual disability have commonly been reported as characteristics associated with Sotos syndrome, and therefore these findings are consistent with the literature. Mean domain standard scores were found to be higher for socialisation and motor skills, suggesting that for this sample these were areas of greater ability compared to communication and daily living skills, although all domain scores were in the low range. To the author's knowledge, adaptive behaviour as measured by the VABS has not been assessed for individuals with Sotos syndrome and therefore this study offers a valuable insight and a more detailed analysis of day to day functioning.

The study identified possible temporal changes in some areas, while other areas appeared to display a more consistent picture over time. No significant differences were revealed in mood, interest and pleasure, repetitive or challenging behaviours. It is encouraging, though, that although the changes were not statistically significant, fewer participants showed challenging behaviours such as self injury, destruction of property and aggression at T2 than T1. This is an encouraging finding in the trajectory of people with Sotos, suggesting that there may be some improvements over time and as individuals grow older. In addition, no participant who had not displayed physical aggression or destruction of property at T1 subsequently showed this at T2. This might indicate that new occurrence of such behaviours beyond a certain age is unlikely.

Impulsivity and Hyperactivity

Data indicated statistically significant reductions in impulsivity and overactivity as measured by the TAQ. Levels of impulsivity and overactivity had previously been comparable to those with ASD (Sheth *et al.*, 2015) and literature has suggested that this may be a common difficulty associated with individuals with Sotos syndrome. However, most research had focused solely on younger participants, with an age range

of 2-16 years (Lane *et al.*, 2016$_b$). The results of this study suggest that hyperactivity and impulsivity may be features of Sotos syndrome more pronounced in children and younger individuals than in older people. The age range at follow-up in the current study was 13-37 years, and most individuals were over the age of 20. Comparison with further groups, such as males with FXS, where evidence shows some reduction in impulsivity over time (Crawford *et al.*, in press), may offer further insight into the nature and specificity of changes.

Autism Spectrum Phenomenology, Communication and Social Interaction

The current study also indicated that behavioural characteristics associated with ASD may have reduced over time. There was a decrease in the proportion of individuals who reached scores indicative of ASD and Autism on the SCQ. At T1, 80% obtained scores suggestive of ASD and 40% of Autism, while at T2, this had reduced to 53.33% of ASD and 26.67% of Autism. Specifically, there was a significant reduction in the reciprocal social interaction domain and the total score of the SCQ, which indicates fewer ASD-related behaviours at the second timepoint. It should be noted that at T2 the 'current' version of the questionnaire was used, whereas at T1 the 'lifetime' version had been used. Since the lifetime version focuses on behaviour at 4-5 years, the comparison with current may not be directly between the ages at the two assessment timepoints. Richards *et al.* (2016) compared these versions of the SCQ and concluded that changes may be reliable and valid, while also acknowledging that it is possible that the change may be reflective of comparing the two versions. Overall, the results suggest that the profile of ASD-related characteristics may not be static over time, and that this warrants further investigation. It may be, for instance, that exposure to more complex social situations with age supports the development of skills in this area, and that the reasons people with Sotos syndrome meet criteria for ASD diagnosis are dependent on developmental stage. Findings build on the results of a cross-sectional study by Lane *et al.* (2016$_a$), who found ASD characteristics of social communication and restricted interests/repetitive behaviours as measured by the Social Responsiveness Scale (Constantino & Gruber, 2012) were most problematic for children aged between 5 years and 19 years, with those over 20 years old showing lower levels of ASD-related traits. With research into genetic syndromes, cross-sectional results such as those of Lane *et al.* are potentially affected by factors such as differences in diagnosis rate between

different age bands. Therefore, the current study, using a longitudinal design, offered useful investigation of these possible changes. Findings would appear to be in contrast to FXS (Lee *et al.*, 2016) and CdLS (Cochran *et al.*, 2015; Moss *et al.*, in press), where research has suggested that ASD symptoms increase with age, while in Cru di Chat syndrome symptoms have been found to remain stable across age groups (Cochran *et al.*, 2015).

Interest in and understanding of differences in sensory experiences has increased in recent years, partly in relation to the inclusion of sensory processing difficulties in the diagnostic criteria for ASD in DSM-V. This is the first study, to the author's knowledge, to specifically assess sensory processing difficulties of individuals with Sotos syndrome. Overall (at the level of total scores on the sensory processing measure), there was little indication that people with Sotos syndrome display higher levels of sensory processing atypicalities than typically developing children. However, data indicated that in the area of 'hyporesponsiveness', 6 of the 15 participants (40%) fell into the range of 'deficiency', as defined by the measure's authors (representing scores more than 2 standard deviations below the mean). This reflects high scores on items involving, for instance, ignoring stimuli such as people calling one's name and sources of physical pain. Average scores in the Sotos syndrome group were also higher than children with developmental disabilities but lower than the group of ASD norms. In addition, three participants (20%) met criteria for 'hyperresponsiveness', involving items such as startling or being alarmed easily by sensory stimuli. Average scores in the Sotos syndrome group for 'hyperresponsiveness' were lower than the developmental disabilities and ASD normative data. In the area of sensory seeking, however, people with Sotos syndrome scored lower (indicating fewer potentially problematic behaviours) than available figures for groups of people with ASD, DD and also typically developing children, indicating that there may be specific areas of atypicality for people with Sotos syndrome, as opposed to generalised sensory processing problems. The current study also found a positive correlation between scores on the SEQ and the SCQ, consistent with the notion that impairments may be related. Understanding of profiles of difference in sensory experience has received little attention in the research literature; future study may be able to offer more detailed characterisation and additional consideration as to its impact on people with Sotos

syndrome. The nature of sensory processing differences with physical features of Sotos syndrome, at the level of specific senses and more central integration/processing of information, has yet to be elucidated. However, the current study indicates that there may be some specific areas in which people with Sotos syndrome may experience difficulties or difference.

Repetitive Behaviours

Results indicated no significant change in repetitive behaviour over time. There continued to be peaks in repetitive questioning and preferences for routine, which suggests that these may be quite consistent characteristics in Sotos syndrome and therefore may be a source of ongoing difficulty for individuals. Sheth *et al.* (2015) had previously found differences in repetitive behaviours of individuals with Sotos syndrome and individuals with DS, PWS and ASD, for example individuals with Sotos scored significantly lower than the ASD group on stereotyped behaviour, but significantly higher than the DS group on repetitive use of language. In summary, the findings relating to social, repetitive and sensory processing difficulties, all broadly related to characteristics associated with ASD, paint a complex picture both cross-sectionally and longitudinally. Continued longitudinal investigation of these factors, and direct assessments in addition to carer-report measures, will be invaluable in future studies.

Challenging Behaviours

Relationships between behaviours that challenge/self-injurious behaviours have been found with other characteristics in some genetic syndromes. For example, in CdLS, FXS and PWS (among others) severity of self-injurious behaviour and behaviours that challenge has been associated with higher levels of impulsivity/overactivity (Arron *et al.*, 2011). Therefore, there may also be a relationship between these behaviours in Sotos syndrome given that both of these characteristics have appeared to reduce. However, given that changes in scores on the CBQ did not reach significance and that research into the behavioural difficulties in Sotos syndrome has tended to focus on children, continued research in this area is warranted. It was also difficult to assess the relationship between challenging behaviours and other characteristics here, as the number of people showing each category of behaviour was low.

Mood and Anxiety

There was no indication of temporal change in mood, interest and pleasure in this study, and indeed no evidence of especially low mood in the group within these results. Scores on the mood domain of the MIPQ-S were found to be similar to those of Angelman syndrome which has been found to have the highest levels of positive effect in one study comparing seven genetic syndromes with a mean score of 21.00 (Oliver *et al.*, 2011). Findings on mood were also reflected in scores on the ADAMS whereby there was no indication of any greater problems with depressed mood than for 'normal' controls. Reports of mood difficulties have been scarce in the available literature of characteristics associated with Sotos syndrome and therefore this offers more evidence that this is unlikely to be a characteristic greatly associated with the syndrome. This contrasts with some genetic syndromes associated with ID, such as CdLS (Nelson *et al.*, 2014), in which low mood is prevalent.

However, data indicated high levels of anxiety in the group, with peaks in the domains of panic and agoraphobia, obsessive-compulsive behaviour and social avoidance. The elevation in obsessive-compulsive behaviour was consistent with scores on the RBQ, and it was also anecdotally reported by parents/caregivers during administration of the ADAMS that their children often engaged in ritualistic and repetitive questioning while anxious. The use of normative data from the SCAS-P and ADAMS illustrated significant differences from typically developing children, including significant differences in agoraphobia and obsessive-compulsive behaviours as measured by the SCAS-P, both with large effect sizes. It is acknowledged that the chronological age group for the normative data of the SCAS-P was lower than the age range of the current sample. However, the measure has been used for people of various ages with ID (Crawford *et al.*, 2017), and developmental age according to the VABS in this study is suggestive of lower abilities with mean age equivalent subdomain scores ranging from 4 years to 10 years. In addition, there was consistency in results between scores on the ADAMS, a measure designed for people with ID, and the SCAS-P, which also indicated significantly higher anxiety (in the form of social avoidance and general anxiety) in the group of people with Sotos syndrome than for people with ID in general, with medium effect size. Comparison with other syndrome groups confirmed anxiety to be high in this group, with individuals with Sotos syndrome displaying significantly higher levels

of generalised anxiety and social anxiety than those with RTS. Although there was a similar age range for participants across groups, they were not matched on key characteristics and therefore future comparisons with well matched groups are required. The current findings also suggested that parents/caregivers of individuals with Sotos syndrome may hold their own needs in relation to their children/people they care for as they grow older. Levels of anxiety and depression, as measured by the HADS, showed higher levels of these characteristics at T2. Cut-off scores are recommended by Zigmond and Snaith (1983). In relation to anxiety cut-off scores, 26.7% of parents obtained scores indicative of 'mild anxiety', 13.3% indicative of 'moderate anxiety' and 6.7% of 'severe' (46.7% in total reaching cut-off scores). In relation to depression cut-off scores, 14.3% parents obtained scores indicative of 'mild depression' and 7.1% of 'severe' (21.4% in total reaching cut-off scores). It was interesting to find that parental anxiety and depression had increased, particularly considering the reduction in levels of impulsivity and overactivity, challenging behaviour and social interaction difficulties. One possible reason for this could be that contributory factors towards parental anxiety and depression could be related more heavily to the characteristics which did not appear to change over time but remained high, such as repetitive behaviours. Alternatively, the increase in children's age may cause an increase in transitions, for example, between schools, day services, adult services, that may increase parental anxiety, and there may be stress caused by increased independence. In addition, Sarimski (1997) has suggested that parental mental health may be related to the rarity of a child's syndrome and the lack of available literature/knowledge that exists. The uncertainty that parents may hold about the future and the long-term trajectory of their children's behaviour may offer some explanation of this increase, where parents have limited knowledge about whether a change in behaviour may be temporary or more permanent. The main sources of anxiety and depression in parents could be more fully explored through qualitative research. Parental HADS scores have been investigated in other genetic syndromes, with both mothers and fathers reaching anxiety cut-off scores in between 14.3-71.4% and depression cut-off scores in between 0-33.3% in samples of those with children with Angelman syndrome, Cri du Chat syndrome and CdLS (Griffith *et al.*, 2011). Perhaps unsurprisingly, total HADS scores also correlated significantly with their children's scores in relation to anxiety, hyperactivity and impulsivity.

This is, to the author's knowledge, the first more comprehensive attempt to formally assess and characterise anxiety in this group. Future research in this area is warranted to describe this profile in more detail and on a greater scale.

2.5.2 Quality and Implications

The current study offers new insights to the literature available on the behavioural phenotype of Sotos syndrome. The findings may be helpful for Clinical Psychologists and other professionals working in the field of neurodevelopmental and genetic conditions to support individuals and their families, to consider their needs and appropriate interventions. The findings indicate the importance of repeated assessment, especially in some areas, of individuals with Sotos syndrome to monitor changes over time to ensure adaptations are appropriate and to enable the impact of impairments on an individual's quality of life to be considered. Reducing levels of impulsivity and overactivity suggest that interventions associated with these behaviours would be helpfully placed in childhood and with younger adolescents.

An implication of the finding that there are reducing numbers of participants reaching scores indicative of an ASD diagnosis suggests that it would be important for those working and assessing people with Sotos syndrome to be cautious of diagnosing ASD too quickly as findings suggest the profile of ASD may change over time. Subtle differences and changes may mean that algorithm-based diagnoses are made too quickly. Furthermore, although tentative (due to the different versions of the SCQ), the reduction in impairments associated with reciprocal social interaction and overall reduction in total SCQ scores may suggest that reciprocal social interaction has a high weighting in scores indicative of ASD in children with Sotos syndrome. Therefore, the assessment and diagnosis of ASD may need to look carefully at specific domains.

In light of findings suggesting that characteristics of repetitive behaviour remain consistent over time there may be important implications for clinical and support services working with people with Sotos syndrome. It may be that interventions proposed for idiopathic ASD may be particularly effective in childhood as repetitive behaviours can become more difficult to change with age, while interventions relating to these behaviours may also be of benefit as people grow older. Training in the understanding of repetitive behaviours would support services and agencies in managing this.

In addition, there may be clinical implications regarding anxiety levels. Routine assessment would support the exploration of this characteristic in more detail. It may also enable people caring for and supporting individuals with Sotos syndrome to have a better understanding of the motivation behind some of the behaviours displayed. Interventions for anxiety may be helpfully placed here while future research is needed to extrapolate further.

2.5.3 Strengths and Limitations

This study represents the first known follow-up in relation to the behavioural phenotype of Sotos syndrome. A strength of the research includes a significant period between the two-time points of data collection. The questionnaires utilised were standardised and the majority of these were appropriate for use with people with ID. The number of questionnaires completed by each parent/caregiver on behalf of each participant offered in-depth information which was followed up by telephone interviews as another opportunity to collect data and this represents a further strength.

It should be noted that although representing a reasonable return rate for a seven-year follow-up, the study had a relatively small sample size. This is a common limitation of research into rare syndrome groups. Despite methods being employed to try to increase the return rate (e.g. reminder letter), there may have been potential barriers which posed as a limitation here, where letters may not have reached all eligible participants and their families due to the amount of time that had passed since the previous study. It is encouraging that no significant differences were found in relation to participants who did and did not participate in the follow-up in relation to age or T1 scores, although this is not a guarantee of the representativeness of the follow-up sample. Retrospective power analyses were calculated following data collection. In light of this being a follow-up study with constraints on recruitment power calculations were not carried out initially. Retrospective calculations indicated that the study was under-powered. The issue of power is a common difficulty within the study of rare syndrome groups and calculation of effect size was hoped to offer indication of the size of the difference independent of sample size. Therefore, the limited generalisability of findings was acknowledged and recommendation for replication has been made. It was also acknowledged that a few of the measures used were not specifically designed for use with people with ID, for example the VABS and the SCAS-P, and therefore this may

represent a limitation in reliable interpretation of these results. The use of these measures was supported by previous research and efforts were made to corroborate findings, for example consistency with other measures (SCAS-P with the ADAMS). Additional limitations are also likely to be similar to those highlighted by Sheth *et al.* (2015), such as the use of retrospective questionnaires which are open to bias and can lack the objectivity of direct assessments. Also, possible recruitment bias in the previous sample was noted by Sheth *et al.* as participants had been recruited from support groups and clinics.

2.5.4 Directions for Future Research

The findings of the current study have offered a valuable follow-up of behavioural and psychological characteristics using a longitudinal design. Given that longitudinal research has been scarce, future research in this area is crucial. It would be beneficial for future research to recruit a larger sample size within a longitudinal design using more in-depth assessments and observational methods. This would support replication of the current study and a larger sample would enable a higher-powered analysis using parametric techniques to be carried out. This would reduce the risk of type 1 errors from the current study due to a small sample size and multiple comparisons.

In addition to replication, two other areas seem particularly important in future research. The use of the ADOS (Lord *et al.*, 2008) and other assessments of ASD may be justified and would carefully characterise changes of phenomenology in more detail. This would add to the understanding of the ASD profile associated with Sotos syndrome. The investigation of anxiety in Sotos syndrome on a bigger scale would also develop the findings of this study and continue to add to the characterisation of the behavioural phenotype. Given the correlations with parent/caregiver levels of anxiety and depression, understanding this profile would support interventions to be made which based on the current results, may impact on the quality of life of parents/caregivers also.

2.5.5 Concluding Remarks

In summary, this study offers a valuable seven-year follow-up of a group of people with Sotos syndrome to demonstrate changes as they have got older. The findings demonstrate a reduction in impulsivity and overactivity over time, with possible decreases in the prevalence of certain challenging behaviours. They also reveal a significant reduction in difficulties associated with reciprocal social interaction, but

continued difficulties with repetitive questioning and preference for routine, suggesting a complex picture of ASD phenomenology across the trajectory. Findings provide evidence of marked anxiety difficulties with people with Sotos syndrome and exploration of this in larger samples would support delineation of this more generally.

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PART 3: CRITICAL APPRAISAL

3.1 Introduction

In this final part of the thesis I will offer a critical appraisal of my journey throughout. I will share some of my reflections of each aspect of the project, from choosing an initial topic to the final write-up, and I will highlight some of my decision-making and the challenges faced along the way. I also hope to share some learning points and the ways I feel I have developed as a researcher. This section has been supported by a research diary maintained throughout the process and supervision notes. I have offered an outline of my epistemological position in Appendix W and an overview of the chronology of the thesis is presented in Appendix X.

3.2 Choosing a Research Topic

This thesis began following the presentation of research interests delivered by my research supervisor. My main hope for the project that I embarked on was that it was valuable and useful in its field. Although I had some initial ideas, I had concerns about recruitment. This led me into the area of genetics which I would certainly acknowledge I was no expert in, but I felt this gave me room to grow and develop as a researcher and a Trainee Clinical Psychologist. The project area that my supervisor presented also provided an opportunity to work with a research centre specialising in the field of neurodevelopmental disorders and genetic syndromes. This was a real advantage in this project and I very quickly became aware that the centre had an excellent reputation in the field of research. During my supervisor's presentation, she spoke about how the area of research often came with a real enthusiasm from geneticists and experts in the field, as well as from participants and their parents/caregivers. I considered how necessary this type of research appeared to be and how valuable it sounded given the rationale for it to be carried out. The potential ease of recruitment, from samples who had already consented to be contacted for future research, also felt like a huge advantage and one that would serve me well. During this phase, I became acutely aware of how my confidence was lacking at the prospect of conducting research on this scale and what lay ahead of me over the course of training. Working with experts in the field increased my confidence in completing a project of this size.

3.3 Planning the Research

Conducting a systematic literature review in my first year of training highlighted some gaps in the area of behavioural phenotypes associated with overgrowth syndromes. This review and discussions with my research supervisor supported the development of a research proposal. In line with the needs of the research centre, the idea focused on investigating the behavioural and psychological difficulties associated with Sotos syndrome at an in-depth level. Given the nature of the topic, a quantitative research approach appeared appropriately selected to enable characteristics to be explored at a largely collective level. I entered the project with a very basic understanding of genetics and the causes of genetic syndromes. I found myself spending a lot of time trying to get to grips with the language used in the literature and there were times when I was certainly left feeling confused and overwhelmed. To aid my understanding, I spent time reading much more broadly about genetics and behavioural phenotypes, as well as liaising with my supervisor in supervision.

As time went on, circumstances forced some changes to be made to the research design. Time was spent discussing this in supervision which took on board time limitations of completing the project. It was quite tricky to manage the uncertainty this led to at times as I know I like to be prepared and very organised. I began working on another project which was the follow-up study detailed in the research report above. This was recruiting participants with the same genetic syndrome and continued to have focus on the behavioural and psychological characteristics associated which meant there was some cross over with materials and my initial literature review. This change in design also meant I could work much more remotely, saving time and monetary resources. Another advantage of this was that the ethics application for this study had already been completed by the research centre as part of a large-scale project. During the planning stages of the project, I had to consider the types of assessments I would be using during data collection. It was imperative that the majority of these were the ones that had been used in the previous study but following anecdotal reports from parents about difficulties with anxiety and ability, it was decided that some additional measures could be completed with participant's parents/caregivers over the phone. This provided the opportunity to speak directly to parents/caregivers and to gather as much detailed information as possible. Time was spent familiarising myself with different measures and it was difficult to find appropriate measures of anxiety and adaptive ability for an

ID population. Reading research into other genetic syndromes and supervision supported me to make decisions about which ones may be the most appropriately selected, including the Vineland Adaptive Behaviour Scales (VABS; Sparrow *et al.*, 2005) and the Spence Children's Anxiety Scale-Parent version (Spence, 2000).

3.4 Systematic Literature Review

Due to the changes within the planning stages of the research, it took a little while to come to a decision about what the literature review would now focus on. My original idea had been a similar review to my first-year literature review on the behavioural phenotype of Sotos syndrome, however I had become aware of a review in this area that had been published very recently. In addition, the changes and the uncertainty about the detailed focus of my research created some difficulty in establishing a topic that would be appropriately linked. This led to a period of searching ideas and topics online and on literature databases. I discussed ideas with my supervisor and other members of the team at the research centre and the idea of carrying out another behavioural phenotype review on another genetic condition was thought to be appropriate. This enabled the overall topics to be linked in relation to the field of behavioural phenotypes. I had enjoyed conducting my first-year literature review into Sotos syndrome, perceiving the area to have quite clear inclusion and exclusion criteria to follow and looked forward to repeating a similar process with Phelan-McDermid syndrome.

As part of the systematic review, I developed skills in using different databases. Consultation with library services supported me to make decisions around which databases to search and the unique search fields to use to maximise the search (based on database options). After beginning the searches, there were times when I started to feel overwhelmed again with my unfamiliarity with medical and genetic language, but through perseverance and careful checking I was able to perform the search and filtering process. The search yielded a high number of papers and there were times when I was unsure if 57 was too many to bring together in one review. Consultation with the research centre and supervision helped me to make the decision that it was reasonable given the topic of behavioural phenotypes to include them all while focusing on the cohort studies. This allowed the encompassing of all available research and maintained clear inclusion and exclusion criteria, as well as considering the limitations of the word count. As such the decision was made to include a summary of the data within case

study papers and to include relevant tables in the appendix. During the process of the systematic review I also developed skills in critical thinking and in using a highly specific quality appraisal tool. With more time, I would have liked data extraction and appraisal to have been repeated by a second independent party to check the ratings allocated to maximise reliability and accuracy. This was not possible due to the limitation of time for the current thesis, however with plans to submit for publication I hope this can be carried out for these purposes. I also often reflected on how I could have written over the allocated word count and I would have liked to have gone into more detail about the genetics and implications. Along with reliability checking, it is hoped this may be considered for the purposes of submission for publication.

3.5 Data Collection

Following the delays and changes that had taken place, I was enthusiastic to get started on participant recruitment and data collection. An initial invitation letter was sent out to participants. Completion of the online survey happened gradually, and I found myself regularly checking the number of completers in anticipation. It was helpful being able to carry out follow up telephone interviews with parents from across the UK and from other countries. This was so important given the rarity of Sotos syndrome and provided the opportunity to recruit more widely at no expense of time and resources. If appropriate to future research projects, I would hope to utilise these methods again. During telephone interviews, I found that parents and carers of participants were very grateful for the research being carried out and telephone interviews tended to last much longer than planned or anticipated due to the amount of information being offered and shared. I tried to achieve a balance of providing additional time to acknowledge enthusiasm, as well as being a researcher with a primary research question. Taking a step away from being a clinician and wanting to capture everything was important at times and I often found myself wondering how much opportunity parents and carers had to tell their stories about their children and the people they cared for. I regularly noticed myself offering empathy to parents and carers, as well as formulating in my head about how behaviours and characteristics of participants may impact on families on a day to day basis. Counselling skills and the process of formulating felt ingrained in my way of listening and thinking about things. I was really encouraged by how enthusiastic the

participants were. I also often reminded myself of my role during the interviews and as these progressed, it felt much easier to focus on being a researcher.

A challenge encountered was trying to navigate offering parents and carers the most convenient time for them to undertake the telephone interviews. This often meant that data collection took place at weekends and during evenings which could be difficult when I had been on my clinical placement in the day. This flexibility was imperative though and enabled so many more people to participate around their employment and family life. I developed good planning skills in relation to how to fit these in around other commitments and fit them in in a way that would allow me to be as attentive and focused as possible.

During data collection, I noticed that at times it was quite difficult using the VABS (Sparrow *et al.,* 2005) as this was a measure that was not specifically designed for use with people with an ID. This survey had been chosen as the best available measure of adaptive behaviour. I often reflected on this during data collection and this was not something I had really appreciated or considered before. Some questions could be adapted, and each interview was different due to varying levels of ID and adaptive ability. While discussing this in supervision, I became aware of how this is a huge limitation in research and work in the area and really highlighted the need for properly developed questionnaires. I was pleased that the majority of the questionnaires I had utilised had been specifically developed for people with ID, a number of which had been developed by researchers at the research centre.

I was able to recruit 17 participants, however two were found to have not completed the first study in 2010. This appeared to represent an error in the database that my recruitment had derived from. I wondered if I could have recruited a larger sample with more time while I did try and maximise this with a reminder invitation letter. It may be possible that the online nature of data collection may have deterred potential parents/caregivers and participants. I think with more time and resources it may have been helpful to try and contact each of the participants who had completed in 2010-2011 by telephone. Additionally, with the research being a follow-up study, participants may have relocated and therefore initial telephone contact may have been beneficial.

Throughout, I also supported the research centre to carry out some direct assessments for the project I had originally been planning to undertake. I was keen to be involved and supportive of this, while also considering the time I needed to allocate to my own project. It was thoroughly enjoyable to meet participants during this time and it gave me face to face contact with people with Sotos syndrome which I was able to draw on while conducting my own research. Once more, I was pleasantly surprised by how open and enthusiastic participants and parents/caregivers were to engage in research.
During the data collection phase, I was also able to learn how to administer a new range of assessment tools and measures. I found it anxiety provoking at times, particularly using the VABS (Sparrow *et al.,* 2005) which I hadn't used before. As time went on, I became much more confident in administering this and using it as a semi-structured interview. I also undertook some training in administering and scoring the Autism Diagnostic Observation Schedule, second version (ADOS-2; Lord *et al.,* 2008) and administering non-verbal assessments of ability. Although I didn't end up using these directly in this research project after all, I have been able to utilise these skills during my placement which has served me well. On reflection, this enabled me to appreciate some more of the transferable skills between clinical practice and research.

3.6 Data Analysis

Data analysis was potentially a challenging phase for me. It seemed some time since I had applied statistical analyses to a 'real life' sample, as opposed to teaching examples. This was very daunting, there was a large dataset to get my head around and I found myself wanting to rush into 'doing' something to it. When considering the type of analysis to use, I had to think very carefully about the sample size. Due to this being small, non-parametric analyses were selected and further advised by my supervisor. Valuable time was saved as the online survey was downloaded into the statistical programme utilised. Along the way I familiarised myself with useful books and manuals, including Pallant (2006) and Field (2013). It was helpful to build on things I had learnt during teaching on statistical analysis. In the future, I feel I should spend more time familiarising myself with my data and considering analytical techniques in advance of the analysis itself. As part of the data analysis process, I developed skills in handling data, inputting onto databases and using statistical software. I often thought about all the different directions I could have taken during data analysis which could

have veered off my initial research questions and it was fascinating to see the potential breadth that one dataset can have. I had to remind myself of my research questions to maintain focus. My main learning point during this phase was the need to approach data analysis in a step by step manner to digest and interpret what findings may mean.

3.7 Write-up

The write-up of each part of the thesis felt like a particularly time-consuming part of the journey and perhaps something that I had completely underestimated. Despite this, it was enjoyable bringing everything together and I engaged more thoroughly in the results and interpretation. I considered it may have been beneficial to have started the write-up phase much earlier rather than allowing this to be carried out in the final few months, although I did make attempts to bring together references and appendices as I went along. This was helpful and something I would hope to continue to do in future research projects. I also think it would be valuable to plan short and long-term goals in order to break down each piece of work and be more rigorous in meeting individual deadlines. Although this was something I had attempted to do, I let things slide much too easily. During the write-up phase, I also found I developed many IT skills and began using shortcuts of which I was previously unaware. These were time-saving applications and will support future research and clinical work.

3.8 Concluding Remarks

I enjoyed engaging in a research project where I had little prior experience and in view of the rarity of Sotos syndrome and Phelan-McDermid syndrome, I feel I have become much more knowledgeable in this area. This enabled me to develop my confidence throughout. I found data collection and engagement with participants the most rewarding phase, while the write-up was more of a 'mountain climb'. I have plans to submit both parts of this thesis for publication and have identified Molecular Autism as a target journal for the systematic review (see Appendix Y). Developing skills of writing concisely and informatively within word counts will support me in future endeavours to engage in research and submit for publication. Overall, completing this thesis has felt like a long process but one that has been ultimately rewarding. I hope the experience and skills acquired in the execution of it will stand me in good stead in my future career as a Clinical Psychologist.

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Part 4: APPENDICES

Appendix A: Case Study Results

Key:
+ = feature/characteristic present,
- = feature/characteristic explicitly stated as not present
Blank = feature/characteristic not mentioned
* = formal psychometric assessment measure used
M = male, F = female, y = years, m = months

Table 27. Characteristics reported within case studies part I

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Anderlid *et al.* (2002)	1	F	33y	Terminal deletion in one of two chromosomes 22. Breakpoint localized in proximal part of n85a3. Size of the deletion estimated to be 100 kb. ACR and RABL2B deleted and proSAP2 disrupted	+	+	-		+ (lack of eye contact, stereotypic movements)	+ (aggressive outbursts)
Artigalás *et al.* (2012)	1	M	10y	1.4 Mb deletion on long arm of chromosome 22 involving ARSA and SHANK3 genes.	+	+	-		+ (restricted social interaction, inflexibility of interests)	

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Babineau *et al.* (2006)	1	F	7y 8m	Recombinant dicentric chromosome 22 containing duplication of the p-arm and pericentromeric regions of q-arm combined with a deletion of 22q13 of 1.75–2 Mb including SHANK3 and ARSA genes.	+	+	+ *Yale Developmental Schedules			
Barakat *et al.* (2004)	1	F	2y	Deletion in distal part of 22q (22q13.31) involving ARSA gene.	+	+	+			
Bartsch *et al.* (2010)	1	F	4y	Deletion of the terminal 5.675Mb (22q13.31~qter; including ~55 genes; NUP50 to RABL2B). karyotype: 46,XX.ishdel(22)(q13.31qter) (ARSA-,N85A-,SHANK3-).	+	+	+			+ (easily irritated)

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Battini *et al.* (2004)	1	M	3y 9m	Ring chromosome 22 encompassing 22q13.3 region. Breakpoint between CTA-299D3 and RP5-925J7 probe, located in 22q13.32. ARSA deleted. Deletion extent estimated to be about 2.5 Mb	+	+ *Griffiths Scale	+		+ (no interest in peers, no social communication, poor eye contact, stereotypic movements, no imitation)	+
Bisgaard *et al.* (2008)	2	M	3y 10m	13q22qter duplication and 22q13.2qter deletion as part of a de novo translocation. ARSA included in the deletion. Final karyotype:46,XY.ishcghdup(13)(q22qter), del(22)(q13.2qter).	+	+	+			
		M	11m	Terminal de novo deletion of 22q of a size of approximately 8.6 Mb. Pseudodeficiency of ARSA. Final karyotype: 46,XY.arr cgh 22q13.2qter(A_16_P21334596/A_16_P03641955) 3 1.			+			

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Bonaglia *et al.* (2006)	1	F	17y	Deletion of chromosome 22q13.3. Breakpoint localised in proximal part of n85a3, containing SHANK3 gene size of deletion estimated at 100 kb.	+	+ *Psycho-Educational Profile-Revised, Vineland Adaptive Behavior Scale	+		+ (poor eye contact, stereotypic hand movements, limited social interaction)	-
Chen *et al.* (2010)	1	M	5y 4m	7.9Mb de novo deletion of chromosome 22q13.2 – qtr. Haploinsufficiency of the SHANK3, NCAPH2 and CYP2D6 genes.	+	+	+		+ (poor eye contact, stereotypic movements)	
Doheny *et al.* (1997)	2	F	1y 10m	Subtelomeric deletion of 22q13.3. Karyotype 46,XX,der(22)t(1;22) (q44;ql 3.32)mat.ish der(22)t(1;22) (D22S39-; D22S39-).	+	+	+			
		F	1y 1m	Subtelomeric deletion of 22q13.3. karyotype 46,XX,del(22) (q13.32).ish del(22)(q13.3ql3.3)(D22S39-) or 46,XX,add(22)(ql3.32).ish del(22)(q13.3 ql3.3)(D22S39-).	+	+	+			

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Goizet *et al.* (2000)	1	F	14y	De novo 22q13.3 deletion.	+	+ *Psycho-educational Profile Revised, WISC-III	+	+ *DSM-IV, Vineland Adaptive Behavior Scale, Childhood Autism Rating Scale		+ (self-aggressive)
Gong *et al.* (2012)	4	M	8y	De novo deletion 22q13.31-33 of size 4387Kb encompassing SHANK3.	+	+	+		+ (impaired social communication, restricted and stereotyped patterns of behaviour)	+ (aggression)
		M	6y 9m	Deletion 22q13.31-33 of size 3673Kb encompassing SHANK3.	+	+	+		+ (poor eye contact, restricted interests)	
		M	2y	De novo deletion 22q13.33 of size 587Kb encompassing SHANK3.	+	+	+		-	
		M	13y	Inherited deletion 22q13.33 of size 113Kb.	+	+	+		-	

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Gorker *et al.* (2016)	1	F	9y	De novo deletion 22q13.3 encompassing MLC1, SBF1, MAPK8IP2, ARSA, SHANK3 and ACR genes.	+	+	+	-		+ (irritability, aggression)
Gustavson *et al.* (1986)	1	M	15y	Monosomic for most of band 22q13	+	+	+			
Karaman *et al.* (2015)	1	M	8m	Karyotype 46, XX,-22,+ r(22)			+		+	
Kim *et al.* (2016)	2	F	1y 5m	Deletion of chromosome 22q13.3. Karyotype 46,XX,del(22)(q13.3). Deletion of ARSA and SHANK3 genes.	+ *Bayley developmental test	+ *Korean infant and child development test, Denver developmental test, Bayley developmental test	+ *Bayley developmental test			
		M	4m	Deletion of chromosome 22q13.3. 46,XX,del(22)(q13.3)	+	+				

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Lam *et al.* (2006)	1	M	7y	De novo ring chromosome 22 with deletion 22q13.3. Karyotype 46,XY,r(22)(p11.2q13.3).	+	+	+		+ (poor eye contact, echolalia and repetitive behaviour)	
Lei *et al.* (2016)	1	F	6y	Novel deletion of 22q13.31q13.33 containing SHANK3 gene.	+	+	+		+	
Lindguist *et al.* (2005)	6	M	6y	Deletion of chromosome 22q13 of size 8.5-9.0Mb.	+	+				
		F		Deletion of chromosome 22q13 of size 5.7-6.0Mb.	+	+	+			
		M		Deletion of chromosome 22q13 of size 4.3-4.5Mb.	+	+	+			
		M		Deletion of chromosome 22q13 of size 4.0-4.1Mb.	+	+			+ (reduced emotional contact)	
		F		Mosaic deletion of chromosome 22q13 of size 5.5-5.7Mb.	+	+	+			
		M	6y	Deletion of chromosome 22q13 with a duplication of size 4.1-4.2Mb.	+	+	+			

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Macedoni-Luksic *et al.* (2013)	1	M	5y	Small microdeletion in chromosome 22q13.3, of size 30 kb encompassing last exon of SHANK3 gene and whole ACR gene.	+	+ *Bayley developmental test	+	+ *DSM-IV	+ (poor eye contact, stereotypic movements)	
Messias *et al.* (2013)	1	F	38y	22q13.33 deletion.		+				-
Misceo *et al.* (2011)	1	F	20y	De novo translo-cation between chromosome Xq21.33 and 22q13.33, associated with a duplication on Xq21.33 and deletion on 22q13.33. Deletion size 17581bp, duplication size 283764bp. The deletion overlaps SHANK3 exons 22 and 23 and ACR.	+	+	+		+ (Stereotypic movements, ritualistic, insists on routine, social interaction difficulties)	+ (anger/throwing objects)
Narahara *et al.* (1992)	1	F	7m	Terminal deletion of the long arm of chromosome 22, del(22)(q13.31).		+	+			

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Passini *et al.* (2010)	1	F	18y	De novo microduplication of 1Mb in 22q13.33 bands and microdeletion involving the last 600Kb of chromosome 22 with an unbalance in the SHANK3/PROSAP2 gene.	+	+	+		+	+ (aggression)
Prasad *et al.* (2000)	3	F	9y 4m	De novo cryptic terminal deletion of 22q13.	+	+ *Gesell Developmental Scale	+	+ *DSM-IV, Childhood Autism Rating Scale		+ (poor cooperation)
		F	8y	Deletion in terminal region of 22q13. karyotype: 46,XX. ish del (22)(q13.3q13.3)(D22S39-).	+	+ *Bayley Scales of Infant Development	+ *Bayley Scales of Infant Development		+ (withdrawn, no imaginative play, difficulty in coping with changes)	+ (aggression)
		M	2y 1m	Deletion of terminal portion of the long arm of chromosome 22 with the breakpoint at 22q13.1. Karyotype: 46,XY, del (22)(q13.1).	+	+ *Gesell Developmental Scale	+		+ (repetitive behaviours, lack of facial expression and eye contact)	

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Schmidt *et al.* (2009)	6	M		22q13 deletion. Karyotype 46,XY, r(22).ish r(22)(p13q13.1)(TUPLE1+, bcr+, ARSA2,Tel22q2).	+	+	+		+	+ (persistent screaming and restlessness)
		F		22q13 deletion. Karyotype 46,XX, del(22)(q13).ish del(22)(q13.3q13.3)(ARSA-).		+				
		F		22q13 deletion. Karyotype 46, XX, del(22)(q13.33).	+		-		+	+ (restlessness and aggression)
		F		22q13 deletion. Karyotype 46, XX, del(22)(q13.32 mos).	+		-		+	+ (aggression and restlessness)
		M		22q13 deletion. Karyotype 46, XY, del (22)(q13.3).	+		+		+	+ (aggression and restlessness)
		F		22q13 deletion. Karyotype: 46, XX, del (22)(q13.3).ish del(22)(q13.3)(ARSA-).	+		+		+	+ (restlessness)
Su *et al.* (2011)	2	M		Unbalanced maternally inherited translocation, partial monosomy 22q13.3 and partial trisomy 15q26.	+	+	+			
		F		Unbalanced maternally inherited translocation, partial monosomy 22q13.3 and partial trisomy 15q26	+	+	+			

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Tabolacci *et al.* (2005)	2	M	24y	Submicroscopic subtelomeric pure deletion of chromosome 22q13, spanning about 3.5Mb from the telomere.	+	+	+		+ (fixed expressions, catatonic-like state)	
		M	15y	Submicroscopic subtelomeric pure deletion of chromosome 22q13, spanning about 3.5Mb from the telomere.	+	+	+		+ (fixed expressions, catatonic-like state)	
Trabacca *et al.* (2011)	1	F	5y	De novo 22q13 monosomy and 2pter duplication, SHANK3 haploinsufficiency was demonstrated. Karyotype 46,XX ish der(22)t(2;22)p(25.3;q13.31)(22qter-,2pterþ). The duplicated 2p and deleted 22q regions span 4.8 Mb and 4.2 Mb, respectively.	+	+	+			

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Verhoeven *et al.* (2013)	1	F	70y	610kb deletion in the distal end of the long arm of chromosome 22 (arr 22q13.33(50,564,18151,175,626) x 1 (Human (GRCh37/hg19) Assembly), comprising 28 known coding genes, including SCO2, TYMP, CHKB, ARSA, and SHANK3.	+	+ *Vineland Screener	+			+
Verhoeven *et al.* (2012)	2	M	29y	2.15 Mb 22qter (22q13.32q13.33) deletion	+	+ *Vineland Screener				+ (temper tantrums)
		M	31y	2.15 Mb 22qter (22q13.32q13.33) deletion	+	+ *Vineland Screener				
Webster & Raymond (2004)	2	F		22q terminal deletion	+ *Pre-school Language Scale-III, The Rossetti Infant-Toddler Language Scale	+	+			+ (aggressive and self-injurious behaviour)
		F		22q terminal deletion	+ *Pre-school Language Scale-III, The Rossetti Infant-Toddler Language Scale	+	+			+ (aggressive and self-injurious behaviour)

Reference	N	Gender	Age	Genetic Information	Delayed Speech and Language	DD/ ID	Delayed Motor Development	ASD	Autistic Features	Behavioural Difficulties
Willemsen *et al.* (2011)	3	M	48y	1.8-Mb loss in chromosomal region 22q13.32q13.33 (47,782,571–49,543,031 Mb).	+	+	+			-
		M	31y	Terminal loss of 2.12 Mb in chromosomal region 22q13.32q13.33 (47,35–49,47 Mb)	+	+	+			+ (aggression)
		M	29y	Terminal loss of 2.12 Mb in chromosomal region 22q13.32q13.33 (47,35–49,47 Mb)	+	+	+		+ (mild obsessive behaviours)	+ (aggressive outbursts)
Total N (%)					**52/57 (91%)**	**51/57 (89%)**	**46/57 (81%)**	**3/57 (5%)**	**24/57 (42%)**	**20/57 (35%)**

Table 28. Characteristics reported within case studies part II

Reference	N	Gender	Age	Genetic Information	Sleep difficulties	Attention and Hyperactivity	Anxiety	Bipolar	Depression	Schizophrenia	Other
Anderlid *et al.* (2002)	1	F	33y	Terminal deletion in one of chromosomes 22. Breakpoint localized in the proximal part of n85a3. Size of the deletion estimated to be 100 kb. ACR and RABL2B deleted and proSAP2 was disrupted.		+ (hyperactivity and concentration problems)					
Bartsch *et al.* (2010)	1	F	4y	Deletion of the terminal 5.675Mb (22q13.31; including 55 genes; NUP50 to RABL2B). karyotype: 46,XX.ishdel(22)(q13.31qter) (ARSA-,N85A-,SHANK3-).			+				+ (severely disturbed sensory perception, high pain threshold)
Battini *et al.* (2004)	1	M	3y 9m	Ring chromosome 22 encompassing 22q13.3. Breakpoint between CTA-299D3 and RP5-925J7 probe, located in 22q13.32. ARSA deleted. Deletion estimated at 2.5 Mb.	+	+ (short attention span)					

Reference	N	Gender	Age	Genetic Information	Sleep difficulties	Attention and Hyperactivity	Anxiety	Bipolar	Depression	Schizophrenia	Other
Bonaglia *et al.* (2006)	1	F	17y	Deletion of chromosome 22q13.3. Breakpoint localised in proximal part of n85a3, containing SHANK3 gene size of deletion estimated at 100 kb.	+		+				
Goizet *et al.* (2000)	1	F	14y	De novo 22q13.3 deletion.	+						+ (high pain threshold)
Macedoni-Luksic *et al.* (2013)	1	M	5y	Small microdeletion in chromosome 22q13.3, of size 30 kb encompassing last exon of the SHANK3 gene and whole ACR gene.		+ (hyperactivity)					+ (toe walking)
Messias *et al.* (2013)	1	F	38y	22q13.33 deletion.			+		+	+	
Passini *et al.* (2010)	1	F	18y	De novo micro-duplication of 1Mb in 22q13.33 bands and microdeletion involving last 600Kb of chromosome 22 with an unbalance in the SHANK3/PROSAP2 gene.	+		+				+ (feeding problems)

Reference	N	Gender	Age	Genetic Information	Sleep difficulties	Attention and Hyperactivity	Anxiety	Bipolar	Depression	Schizophrenia	Other
Prasad *et al.* (2000)	3	F	9y 4m	De novo cryptic terminal deletion of 22q13.							
		F	8y	Deletion in terminal region of 22q13.							+ (sexual behaviour)
		M	2y 1m	Deletion of terminal portion of the long arm of chromosome 22 with the breakpoint at 22q13.1.							+ (sensitivity to certain textures)
Schmidt *et al.* (2009)	6	M		22q13 deletion. Karyotype 46,XY, r(22).ish r(22)(p13q13.1)(TUPLE1+, bcr+, ARSA2,Tel22q2).	+						
		F		22q13 deletion. Karyotype 46,XX, del(22)(q13).ish del(22)(q13.3q13.3)(ARSA-).							
		F		22q13 deletion. Karyotype 46, XX, del(22)(q13.33).		+ (short attention span)					
		F		22q13 deletion. Karyotype 46, XX, del(22)(q13.32 mos).							+ (high pain threshold)

Reference	N	Gender	Age	Genetic Information	Sleep difficulties	Attention and Hyperactivity	Anxiety	Bipolar	Depression	Schizophrenia	Other
		M		22q13 deletion. Karyotype 46, XY, del (22)(q13.3).		+ (short attention span)					
		F		22q13 deletion. Karyotype: 46, XX, del (22)(q13.3).ish del(22)(q13.3)(ARSA-).							
Tabolacci *et al.* (2005)	2	M	24y	Submicroscopic subtelomeric pure deletion of chromosome 22q13, spanning about 3.5Mb from the telomere.							+ (high pain threshold)
		M	15y	Ssubmicroscopic subtelomeric pure deletion of chromosome 22q13, spanning about 3.5Mb from the telomere.							+ (high pain threshold)

Reference	N	Gender	Age	Genetic Information	Sleep difficulties	Attention and Hyperactivity	Anxiety	Bipolar	Depression	Schizophrenia	Other
Trabacca *et al.* (2011)	1	F	5y	De novo 22q13 monosomy and 2pter duplication, SHANK3 haploinsufficiency was demonstrated. The duplicated 2p and deleted 22q regions span 4.8 and 4.2 Mb.		+ (Attention Deficit Disorder)					+ (high pain threshold)
Verhoeven *et al.* (2013)	1	F	70y	610kb deletion in distal end of the long arm of chromosome 22, comprising 28 known coding genes, including SCO2, TYMP, CHKB, ARSA, and SHANK3.	+		+	+			+ (high pain threshold)
Verhoeven *et al.* (2012)	2	M	29y	2.15 Mb 22qter (22q13.32q13.33) deletion	+	+ (hyperactivity)	+	+ *International Classification of Diseases-10	+		+ (disinhibited behaviours)
		M	31y	2.15 Mb 22qter (22q13.32q13.33) deletion				+	+		
Webster & Raymond (2004)	2	F		22q terminal deletion	+						
		F		22q terminal deletion	+						

Reference	N	Gender	Age	Genetic Information	Sleep difficulties	Attention and Hyperactivity	Anxiety	Bipolar	Depression	Schizophrenia	Other
Willemsen *et al.* (2011)	3	M	48y	1.8-Mb loss in region 22q13.32q13.33 (47,782,571–49,543,031 Mb).							
		M	31y	Terminal loss of 2.12 Mb in region 22q13.32q13.33 (47,35–49,47 Mb)	+			+			+ (high pain threshold)
		M	29y	Terminal loss of 2.12 Mb in region 22q13.32q13.33 (47,35–49,47 Mb)	+	+ (hyperactivity)		+	+		+ (high pain threshold)
Total N (%)					**11/57 (19%)**	**8/57 (14%)**	**6/57 (11%)**	**5/57 (9%)**	**4/57 (7%)**	**1/57 (2%)**	

Appendix B: Data Extraction Guide

1. Title and author

2. Participant details (How many participants are there? How many are males and females? How old are participants? What is the age range?)

3. Participant recruitment (How was the sample identified? How were they recruited?)

4. Participant diagnoses and genetic details (How were diagnoses made? Was any molecular/cytogenetic/metabolic testing carried out? What genetic information is available?)

5. Behavioural and psychological characteristics (What characteristics did the paper report on? What relevant findings are there?)

6. Assessment measures used (How was each characteristic measured?)

7. Comparison group (Did the paper use a comparison group? What are the details of the group? How were they matched?)

Appendix C: Quality Appraisal Tool

Table 29. Quality appraisal tool

	Quality Rating 0 Poor	1 Adequate	2 Good	3 Excellent
Sample Identification	Not specified/reported	Single restricted or non-random sample e.g. a specialist clinic or previous research study Single regional sample e.g. a regional parent support group	Multiple restricted or non-random samples e.g. multi-region specialist clinics National non-random sampling e.g. national parent support groups	Random or total population sample
Confirmation of syndrome	Not confirmed/reported Clinical diagnosis only suspected	Clinical diagnosis by 'generalist' e.g. General Practitioner or Paediatrician Confirmed previous diagnosis with genetic details[16]	Clinical diagnosis by 'expert' e.g. Clinical Geneticist or Specialist Paediatrician	Molecular/Cytogenetic/ Metabolic confirmation of diagnosis
Behavioural/ Psychological Assessment[16]	Not specified/reported Clinician judgement only	Screening instrument e.g. Social Communication Questionnaire Informant report measure e.g. Vineland Adaptive Behaviour Scale[16] Clinician judgement against specified diagnostic criteria e.g. DSM-IV or ICD-10 Report of previous diagnosis with method[16]	Diagnostic instrument e.g. ADOS, WAIS, WISC Direct formal assessment[16]	Consensus from multiple assessments, including at least one diagnostic/direct formal instrument[16]

[16] Marks areas where criteria were adapted to meet the requirements of this review.

Appendix D: Cohort Studies

Table 30. Study characteristics for cohort studies

Reference	N	Gender (F, M)	Age range (years)	Participant recruitment	Genetic information	Characteristics reported/measured	Comparison group
Bro *et al.* (2017)	193	Available on 162 participants 87M 75F	<1 to >40	Phelan-McDermid Syndrome Foundation	Diagnosis of PMS – not confirmed as part of the study	Sleep	Comparison of mean scores with a clinical sample of children aged 4–10 years diagnosed with a sleep disorder and a community sample of children aged 4–10 years enrolled in public elementary schools from another study.
Denayer *et al.* (2012)	7	3M 4F	5-51	Genetic Department in Belgium (random sample of ID)	The genomic DNA of the participants was screened using the BAC/PAC-array or the Oxford Gene Technology (OGT) CytoSure TM ISCA oligoarray set containing either 105k or 180k DNA oligonucleotides with a minimum resolution of 200 kb by a Clinical Geneticist. 22q13 microdeletions identified. Deletion sizes ranged from 76Kb-3.4Mb. Gene content SHANK3 in all participants.	ADHD Autistic features Behavioural features Developmental level Mental health Motor skills Speech and Language	None
Dhar *et al.* (2010)	13	6M 7F	3-19	Genetic Department in the USA (random sample of genetic samples)	Array-based comparative genomic hybridization, higher resolution aCGH (244k) and FISH analyses showed terminal deletion 22q13.3 with sizes from 95Kb to 8.5Mb. Two had partial deletions of SHANK3 with proximal breakpoints located within the gene. Ten had complete deletions of SHANK3. One had deletion of ARSA and SHANK3.	ASD and autistic features Behavioural features Developmental level Sleep Speech and language	None

Reference	N	Gender (F, M)	Age range (years)	Participant recruitment	Genetic information	Characteristics reported/measured	Comparison group
Egger *et al.* (2016)	7	3M 4F	22-44	Genetic Department in the Netherlands	Phelan Mcdermid syndrome with deletion size ranging between 63Kb-2.15Mb. SHANK3 confirmed to be deleted in one participant who was reported to have been evaluated using microarray analysis.	Developmental level Mental health Motor skills Speech and Language	None
Glaser & Shaw (2011)	18	9M 9F	5-18	22q13 Deletion Syndrome Support Group (national)	Diagnosis of 22q13 Deletion syndrome from a pediatrician, psychiatrist/psychologist, or neurologist (no other information given).	Developmental level	Comparison group of 19 children with diagnosis of Autism
Kolevzon *et al.* (2014)	9	3M 6F	5-15	Ongoing research studies at Seaver Autism Centre for Research	Chromosomal microarray or high throughput or targeted sequencing confirmed all participants had PMS and with SHANK3 deletions or mutations.	ASD Developmental level	None
Koolen *et al.* (2005)	9	4M 5F	Not specified	Genetic clinical departments in France, Ireland, the United Kingdom, and the Netherlands	High-resolution chromosome specific array-based comparative genomic hybridisation confirmed subtelomeric deletions of 22q13 (seven with a submicroscopic 22qter deletion, one with an unbalanced translocation and one with a microscopically visible 22qter deletion). The deletion sizes varied between 8.4Mb with the breakpoint mapping to 22q13.2 and the smallest deletion spanning 3.3Mb with the breakpoint mapping to 22q13.31.	Developmental level Speech and language	None

Reference	N	Gender (F, M)	Age range (years)	Participant recruitment	Genetic information	Characteristics reported/measured	Comparison group
Luciani *et al.* (2003)	33	16M 17F	1-36	Unknown	Characterisation of the deleted material was done by fluorescence in situ hybridisation (FISH). All participants had a "pure" partial 22q13 monosomy. There were seventeen participants with an r(22) chromosome, twelve had a simple terminal 22q13 deletion, four had an unbalanced translocation involving an acrocentric short arm and were considered as ‘‘pure’’ 22q13 monosomies.	Behavioural features Developmental level Speech and language	None
Manning *et al.* (2004)	11	1M 10F	0.4–46	Genetic departments in USA (random sample of genetic samples)	Cytogenetic analyses and FISH confirmed all had deletion of the 22q13.3 band. In 6 a microscopically visible de novo deletion of band q13.3 was observed. While 5 had deletions of band q13.3 from inheritance of the unbalanced meiotic disjunction products of a parental translocation.	Autistic features Developmental level Speech and language	None
Mieses *et al.* (2016)	24	Unreported	2-11	Ongoing studies at the Seaver Autism Center for Research	Chromosomal microarray (CMA) or Sanger sequencing confirmed all participants had a diagnosis of PMS with confirmed deletion or mutation of SHANK3.	ASD Developmental level Sensory experiences	Comparison group of 61 children with idiopathic ASD
Nesslinger *et al.* (1994)	7	4M 3F	2-5	Genetic departments and hospitals across Toronto, Houston, Philadelphia, Ohio and Miami.	De novo deletions of Chromosome 22q13.3 identified by high resolution cytogenetic analysis. The proximal breakpoints of the deletions varied between loci D22S92 and D22S94. The most distally mapped locus, ARSA was deleted in all.	Developmental level Motor skills Speech and language	None

Reference	N	Gender (F, M)	Age range (years)	Participant recruitment	Genetic information	Characteristics reported/measured	Comparison group
Oberman *et al.* (2015)	40	25M 15F	3-18	Phelan-McDermid Syndrome Foundation	Diagnosis was based on clinical reports supplied by the parents. Thirty-one had deletions affecting the 22q13 region of chromosome 22. Two had complex chromosomal rearrangements including a deletion in 22q13 region of chromosome 22. Three had 22ring chromosomes. One had an unbalanced translocation involving chromosomes 22 and 18. And One had a point mutation in 22q13 region of chromosome 22.	ASD and autistic features Developmental level Speech and language	None
Phelan *et al.* (2001)	37	17M 20F	1-26	Deletion 22q13 Support group in South Carolina (regional)	Medical records of chromosomal analyses and chromosomal analyses using blood tests. 29 terminal deletions and 8 unbalanced translocations. All the breakpoints of the terminal deletions were within 22q13, with 26 individuals determined to have breakpoints in 22q13.3, 2 individual having breakpoints within 22q13.2, and 1 mosaic individual with the sub-band unspecified. One individual with a terminal deletion of 22q13.3 also had a satellited Y chromosome. Two individuals with del(22)(q13) were mosaic—one with a second cell line containing a ring chromosome 22 and the other (mentioned previously as having the sub-band unidentified) with a second cell line having an apparently normal chromosome constitution.	ASD and autistic features Developmental level High pain threshold Motor skills Speech and language	None (Some comparison to 24 previously reported cases)

Reference	N	Gender (F, M)	Age range (years)	Participant recruitment	Genetic information	Characteristics reported/measured	Comparison group
Philippe *et al.* (2008)	8	5M 3F	5-8.4	Unclear	FISH analyses revealed all were found to be carrying a 22q13.3 deletion. Size of deletions spanned from 150kb to 9mb. Four had a deletion within intron 8 of SHANK3 gene, four had deletion that extended beyond SHANK3.	ASD Behavioural features Developmental level Motor skills Sensory experiences Speech and language	None
Rankine *et al.* (2017)	18	8M 10F	2.5-14.3	Ongoing studies in PMS at the Seaver Autism Center for Research	Diagnosed with PMS using chromosomal microarray or sequencing	ASD and autistic features Speech and language	None
Reierson *et al.* (2017)	50	25M 25F	4-48	Ongoing research studies, a genetics department in the USA and support groups.	Diagnosed with PMS – not confirmed as part of the study	Developmental level	None (Some comparison to previously reported cases)
Sarasua, Boccuto *et al.* (2014)	201	81M 120F	0.4-64.2	Phelan-McDermid Syndrome Foundation conferences	High-resolution 22q12q13 array CGH confirmed PMS. Of the 120 individuals with a custom 22q13 microarray, 89 % were 22q13 terminal deletions; accompanied by proximal duplications (9 %), and interstitial deletions (2 %). Deletion breakpoints varied across the 9-Mb terminal region of 22q13. The interstitial deletions did not include SHANK3. 14 with ring 22 and 9 with deletions associated with unbalanced translocations. Eleven had terminal deletions with duplication preceding the deletion breakpoint. For those with a duplication and terminal 22q13 deletion, duplication sizes ranged from 0.02 to 6.84 Mb with a median of 1.3 Mb.	ASD Behavioural features High pain threshold Motor skills Sensory experiences Sleep Speech and language	None

Reference	N	Gender (F, M)	Age range (years)	Participant recruitment	Genetic information	Characteristics reported/measured	Comparison group
Sarasua, Dwivedi *et al.* (2014)	70	29M 41F	0.4-40	Phelan-McDermid Syndrome Foundation conferences	Customized oligo array comparative genomic hybridization confirmed terminal deletions on 22q13, deletion sizes ranging from 0.2 to 9.2 Mb. All participants have a terminal deletion encompassing the SHANK3 gene and all but two are also missing one copy of IB2.	ASD Behavioural features Motor sills Sensory experiences Speech and language	None
Sarasua *et al.* (2011)	71	29M 42F	0.4-40	Phelan-McDermid Syndrome Foundation conferences	Custom-designed high-resolution oligonucleotide array comparative genomic hybridisation platform with a resolution of 100 bp to identify participants diagnosed with PMS with a terminal deletion encompassing the SHANK3 gene. Deletion sizes were highly variable, ranging from 0.22 to 9.22 Mb.	ASD Behavioural features Developmental delay Speech and language	None
Shaw *et al.* (2011)	35	14M 21F	2.3-41	22q13 Deletion Foundation (national)	FISH analysis confirmed simple 22q13 deletion.	ADHD ASD Behavioural features Developmental level Mental health	None
Soorya *et al.* (2013)	32	18M 14F	1.6 - 45.4	Phelan-Mcdermid Syndrome Foundation and ongoing research studies	CMA and MLPA were used to confirm previous clinical genetic testing. 22q13.3 deletions ranging in size from 101kb to 8.45mb and two participants with de novo SHANK3 mutations. All participants had confirmed SHANK3 deficiency secondary to mutation or deletion.	ADHD ASD and autistic features Behavioural features Developmental level High pain threshold Motor skills Sleep Speech and language	None

Reference	N	Gender (F, M)	Age range (years)	Participant recruitment	Genetic information	Characteristics reported/measured	Comparison group
Wang *et al.* (2016)	11	6M 5F	Mean 7.9	Phelan-McDermid Syndrome Foundation and ongoing studies at the Seaver Autism Center for Research	Diagnosed with PMS with SHANK3 deletions or mutations, confirmed using chromosomal microarray (CMA) or Sanger sequencing.	ASD Developmental level Speech and language	Comparison group of 9 children with idiopathic ASD
Wilson *et al.* (2003)	56	Not reported	Unreported	Deletion 22q13 Support group (regional)	FISH analysis confirmed deletion of 22q13. The deletions were found to vary in size from 130kb to greater than 9 Mb, but all cases that could be analysed for the terminal 130 kb region containing SHANK3 showed a deletion of this gene (45/56).	Behavioural features Developmental level Speech and language	None
Zwanenburg *et al.* (2016)	33	9M 25F	0.6-14.9 (at first assessment), 1.1-15.75 (at second assessment)	Genetic departments and university medical centres across the Netherlands	Diagnosed with 22q13.3 deletion syndrome including SHANK3, confirmed using high resolution array. Deletion sizes ranged from 182 kb to 9.2 Mb. Four children had a small deletion of 182 to 224 kb that includes only three OMIM genes: SHANK3, ACR, and RABL2B. Twenty-three children had a medium sized deletion ranging from 377 kb to 6.6 Mb, and five children had a larger deletion ranging from 7.3 to 9.2 Mb extending beyond the PARVB gene. Three children had an additional copy number variation (CNV) of another chromosome, five children had a deletion caused by a ring chromosome 22 and one child had a mosaic terminal deletion.	Developmental level Motor skills Speech and language	None

Appendix E: Initial REC Ethics Approval Letter

[redacted] Research Ethics Committee
[redacted]

22 February 2010

Telephone [redacted]
Facsimile [redacted]

[redacted]

Dear [redacted]

Study title: **Understanding Behaviour and Family Adjustment in Individuals with Neurodevelopmental Disorders.**
REC reference: **10/H1210/1**
Protocol Number: **Version 1**

Thank you for your letter of 02 February 2010 responding to the Committee's request for further information on the above research and submitting revised documentation. Please accept my sincere apologies for the delay in writing to you the IT problem with the Research Ethics Database has only been fixed today.

The further information has been considered on behalf of the Committee by the Chairman.

Mental Capacity Act 2005

The members of the committee present approved the supplementary application on the basis described in the documentation submitted. I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Confirmation of ethical opinion

The research continues to have a favourable opinion from this committee. It should continue to be conducted on the basis previously approved by the committee, as amended by this supplementary application. The conditions of approval issued with the committee's original favourable opinion continue to apply.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter	[redacted]	14 December 2009
REC application	IRAS	11 December 2009

Protocol	Version 1	01 December 2009
Copy REC letter		06 November 2009
Investigator CV	[redacted]	10 December 2009
Letter of invitation to participant	Version 1 A31 Letter Unknown new research project	10 December 2009
Letter of invitation to participant	Version 1 A31 Letter Known new phase of research	10 December 2009
Questionnaire: Instructions & Background Information	Version 1	10 December 2009
Questionnaire: Wessex		
Questionnaire: Social Communication		
Questionnaire: Activity		
Questionnaire: Sociability for People with Intellectual Disabilities		
Questionnaire: Health		
Questionnaire: Mood Interest & Pleasure		
Questionnaire: The CBQ		
Questionnaire: Parenting & the Family		
Questionnaire: Your feelings & emotions		
Questionnaire: Nisonger Scale		
Questionnaire: Brief-P		
Questionnaire: The RBQ		
Questionnaire: Food Related Problems		
Questionnaire: Routines Inventory		
Questionnaire: The GRQ		
Questionnaire: NCCPC-R Pain Checklist		
Questionnaire: Social Resources		
Letter of invitation to participant	Continue Project version 1 A31 Letter	10 December 2009
The Fragile X Society syndrome group letter of support		01 June 2009
Participant Information Sheet: A31 Consultee	Version 1	10 December 2009
Participant Information Sheet: Symbol	Version 1	10 December 2009
Participant Consent Form: Access to Medical Records	Version 1	10 December 2009
Assessment of Capacity Protocol	Version 1	10 December 2009
Interview Schedules/Topic Guides	Vineland-II Adaptive Behaviour Scales 2nd Edition	
Interview Schedules/Topic Guides	Challenging Behaviour Interview	
Evidence of insurance or indemnity	UMAL Certificate of	01 August 2009

Covering Letter	[redacted]	02 February 2010
Participant Consent Form: A31 Consent Known Form B	Version 2	01 February 2010
Participant Consent Form: A31 Consent Unknown Form A	Version 2	01 February 2010
Participant Consent Form: A31 Consent Form Unknown Form B	Version 2	01 February 2010
Participant Consent Form: A31 Consent Unknown Form C Consultee	Version 2	01 February 2010
Participant Consent Form: A31 Confirm Known Form A	Version 2	01 February 2010
Response to Request for Further Information		
Participant Information Sheet: A31 Infor fu 16+	Version 2	01 February 2010
Participant Information Sheet: A31 Info Unknown 16+	Version 2	01 February 2010
Participant Information Sheet: A31 infor Fu <16	Version 2	01 February 2010
Participant Information Sheet: A31 Info Unknown <16	Version 2	01 February 2010
Participant Consent Form: A31 Consent Known Form C	Version 2	01 February 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nationalres.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

10/H1210/1 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

[redacted]

[redacted]

Chairman

E-mail: [redacted]

Copy to: [redacted]

Appendix F: HRA Amendment Approval Letter

NHS
Health Research Authority

[redacted]

01 December 2015

[redacted]

Dear [redacted]

Study title:	**Understanding Behaviour and Family Adjustment in Individuals with Neurodevelopmental Disorders.**
REC reference:	**10/H1210/1**
Protocol number:	**RG_09-081**
Amendment number:	**Substantial Amendment 3 23.09.2015**
IRAS project ID:	**20638**

The above amendment was reviewed on 27 November 2015 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Substantial Amendment 3 23.09.2015	
Other [Autism Catatonia Questionnaire]	1	23 September 2015
Other [OG-575 Salvia Self-Collection Manufacturer's Instructions]	1	23 September 2015
Other [A31_inforfu_over16]	4	23 September 2015
Other [A31_inforfu_under16]	4	23 September 2015

Other [A31_infoknown_over16]	4	23 September 2015
Other [A31_infoknown_under16]	4	23 September 2015
Other [A31_infounknown_over16]	4	23 September 2015
Other [A31_infounknown_under16]	4	23 September 2015
Other [A31_consentknownA]	5	23 September 2015
Other [A31_consentknownB]	5	23 September 2015
Other [A31_consentknownC]	5	23 September 2015
Other [A31_consentunknownA]	5	23 September 2015
Other [A31_consentunknownB]	5	23 September 2015
Other [A31_consentunknownC]	5	23 September 2015
Other [A31_Coverletterfu_salivacollection]	1	23 September 2015
Research protocol or project proposal	4	23 September 2015

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

10/H1210/1:	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Chair

E-mail: [redacted]

Enclosures: *List of names and professions of members who took part in the review*

Copy to:

Appendix G: Initial Invitation Letter

[redacted] [redacted]

July 2018.

Dear «Title_of_carer»«Surname_of_carer»

You may remember that you have previously taken part in our research here at the [redacted], by completing questionnaires about the person you care for «Participant_first_name». We would like to thank you again for this, and hope you found the feedback that we sent to you helpful. We are now extending this project by carrying out a 6-7 year follow-up via an online questionnaire to find out about changes since we last contacted you. We will follow the online questionnaire with a phone call to ask in some more detail about «Participant_first_name» and their skills and abilities. You may also have the opportunity (which would be optional) for «Participant_first_name»to provide a saliva sample for genetic analysis. The results of this study will be important for understanding how people with Sotos syndrome change as they grow older. This is particularly important because there is little known about the changes in the behavioural phenotype of Sotos syndrome, and the information we gather may help guide interventions for any behavioural difficulties that may occur. Currently, very little is known about how people with Sotos syndrome progress and change over time. The more people that take part in this research, the more meaningful the results are. A good response at this follow-up will provide new and valuable information concerning age related behaviour changes seen in Sotos syndrome.

You have previously expressed an interest in being part of our research; if you are still interested in taking part, we would greatly appreciate if you could complete this follow up questionnaire. Please type the website address below into your internet browser. This will take you to a webpage where you can find out more information about this questionnaire and chose whether or not you would like to take part.

https://tinyurl.com/yatbmzne

Your login details are presented below, please enter these when directed.

Password: [redacted]
ID: «Universal_ID»

Further information about the questionnaire will be available when you log in using this link. We would also like to ring you on the telephone to ask you some questions about «Participant_first_name»and their abilities, strengths and difficulties, when the questionnaires are complete.

If you have any queries about this questionnaire, or any difficulties accessing the survey, please contact [redacted] A.Welham@bham.ac.uk [redacted] Thank you for your continued support of our research.

Yours sincerely

[redacted]

Appendix H: Participant Information Sheet from Online Survey

[redacted] [redacted]

Understanding behaviour in Neurodevelopmental Disorders: Information Sheet

Please read this information carefully before deciding whether you wish to take part in the study. If you have any further questions, please contact [redacted] If you have any medical/ other problems which make it difficult for you to read this information, please contact [redacted] for a verbal explanation of the research.

When you are happy that you have all of the information you need to be able to decide whether or not you and the person you care for would like to take part in the study, please complete the online consent form and questionnaire pack.

Background

You may remember that you have taken part in our research before by completing questionnaires about the person you care for. We hope you found the feedback that we sent to you helpful. We would like to invite you to take part in a follow-up questionnaire study being conducted at the [redacted]. This research work, which is led by [redacted], looks at a range of behaviours, skills and impairments in individuals with Sotos syndrome including: Repetitive behaviour, Hyperactivity, Mood, Challenging behaviour, Social functioning and Health. We will also ask some questions that are related to family well-being and the impact that having a child with a disability has on the family.

We hope that this information will enable us to further understand the behaviours, skills and impairments associated with Sotos syndrome including challenging behaviour, social functioning, mood, hyperactivity and health and the impact that these behaviours have on the family. The more people that take part in this research, the more meaningful the results will be. A good response will provide new and valuable information about Sotos syndrome.

Aims of the study

1. To further our understanding of challenging behaviour, repetitive behaviour, hyperactivity, mood and social functioning in individuals with Sotos syndrome.
2. To understand what happens with regard to these behaviours as children and adults develop.
3. To understand what, if any, changes may occur with regard to these behaviours when the individuals reach a certain age.
4. To understand the impact of having a child with a disability has on the family.

What will happen if you and your child/the person you care for decide(s) to participate?

Where will the research take place?

The research will involve completing the online questionnaire pack. This can be completed by you in your own time.

Who will be involved in collecting the data?

Members of the research team at [redacted]

How long will participation in the study take?

The questionnaire pack will take approximately 45 minutes to complete.

After you have completed the questionnaire, we will contact you again in order to clarify any information that you have provided and to ask you for further information regarding the person you care for. This helps us to ensure that our data is as useful and as accurate as possible.

What will participants be required to do during the study?
We will ask parents and caregivers to complete the online consent form and questionnaire.

Are there any risks that individuals taking part in the study might face?
There will not be any risks associated with completing the online questionnaire. You are free to withdraw from the study at any time, including if your child/person you care for becomes upset or unhappy.

What are the potential benefits for participants from taking part?
You will receive a personalised feedback regarding your child/ the person you care for based on the online questionnaire. This study will also help us to find out more about the people with Sotos syndrome and the genetic variation that may be important for understanding causes and consequences of the syndrome. The results might help us to improve things for people with Sotos syndrome in the future.

Where will data be stored?
The data collected will be kept in password protected storage at the [redacted] and on servers in the high security data centres of our survey-hosting partner (LimeSurvey). Information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998. Only researchers directly involved in this study will have access to the information collected. In any sort of study we might publish, we will not include any information that will make it possible to identify a participant.

If you/ the person you care for decide(s) to participate, what will happen after that participation?
You and your child/ person you care for will receive an individual feedback report describing the results of all of the assessments that were carried out during the study. If requested, this feedback report will be circulated to other interested individuals. Descriptions of research findings will be published in newsletters of the relevant family support groups and educational institutions involved. Any request for advice concerning the person you care for will be referred to [redacted].

The researchers will publish the findings from the study in scientific journals and will present the results at relevant conferences.

What will happen to the data afterwards?
The information that you provide will be held on password protected databases and on high security servers at the [redacted]. Participants will be identified by a unique number so that the information you provide us with cannot be traced to your personal details. You will be able to decide whether or not you want to make your research data available to any professionals or clinicians working with you and the person you care for should they wish to see it. This is optional and will not affect your participation in the current study. If you agree to this, then your research data will only be made available to relevant clinicians or professionals should they contact us directly and request to see it. If you do not agree to this then research data will not be made available to anyone other than the research team at the [redacted].

What will happen to my personal details afterwards?
Since you have previously been involved in our research projects at the [redacted] and have agreed to be contacted by the research team with information about future research work, we have a copy of your personal details on the 'Regular Participant Database'. This database is password protected and only approved members of our research team have access to your details. We do not share your details with anyone outside the research team.

What happens if I decide that I no longer want my details on the Regular Participant Database?
All you would need to do is contact [redacted] or at the [redacted]. Your details would be removed from the database immediately.

Consent
After having read all of the information and having received appropriate responses to any questions that you may have about the study you and the person you care for will be asked to give your and your child's/ person you care for's consent to participate in the study if you decide that you do wish to participate. The section below on ***'Giving consent'*** will explain this process. We need to receive consent from/ on behalf of potential participants in order for them to participate.

Withdrawal
Even after consent has been granted, participants can request to be withdrawn from the study at any time, without giving a reason. Even after participation has taken place, consent can be withdrawn and any data collected will be destroyed. This will not restrict the access of you/ the person you care for to other services and will not affect their right to treatment.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact [redacted] in the first instance. If you remain unhappy and wish to complain formally, you can contact: [redacted] by email: [redacted]

Confidentiality

The company with whom we have chosen to host our questionnaires (Limesurvey) adheres to stringent security practices. However, the transmission of data over the Internet can never be guaranteed to be entirely secure. By taking part in this study the risk to your personal information is no greater than at any other time that you provide this information online (e.g. shopping, banking). Nevertheless, please participate in this research only if you are comfortable with this.

If details from the study are published, information on participants will be presented without reference to their name or any other identifying information. All personal details held at the [redacted] will be kept separately from the information collected so that it will only be possible to connect results to individuals via a special code. This will ensure that results are kept anonymous. In the unlikely event of any evidence of abuse being identified, this information will be disclosed to you by the research workers

Review
The study has been approved by [redacted] NHS Research Ethics Committee. For any queries or concerns regarding the ethical approval of this study please contact [redacted] quoting study reference number: 10/H1210/1.

Further information
If you would like any more information about the study, please contact [redacted] Or write to [redacted]

Giving consent

Now it is up to you whether you decide that you and your child/the person you care for would like to participate. The decision about whether or not to take part in the study must be 'informed'. This means that anyone making the decision must understand exactly what is involved in the study, what will be required from participants and why.

IMPORTANT:

You need to decide whether your child/the person you care for is able to understand enough about the study to make an 'informed' decision independently about whether or not they would like to participate and to communicate this decision to you. If you are unsure whether or not your child/person you care for is able to understand enough to make a decision independently then we can provide you with some guidelines to help you to assess this. A symbol information sheet can also be made available to you if this would be of help. Please contact [redacted] to request a copy of

Please choose from one of the following options:

1. **If your child/ the person you care for is <u>able to understand</u> what is involved in the study and what will be required from them if they participate and has communicated this decision to you, please check this box** ☐

   Please check this box if you think that the person is ***<u>is</u>* <u>able</u>** to understand enough about the study in order to make an 'informed' decision and they decide that they would like to participate. Please ensure that they complete **Section 1** of the consent form. A parent/carer will need to complete **Section 2** of the consent form in order to indicate that they also agree to participate in the study. A symbol information sheet can be made available in order to support your child/person you care for in making this decision if it would be of help. Please contact the research team if you would like a copy of the symbol consent form or if you need us to adapt this information further in order to suit your child's needs.

OR

2. **If you child/ the person you care for is <u>unable to understand</u> what is involved in the study and what will be required from them if they participate (either because they are too young to understand or because they are unable to understand) and cannot communicate their decision to you, please check this box** ☐

   Please check this box if you are reading this information on behalf of someone you care for who is under the age of 16 years and you decide that the person ***<u>is not</u>*** able to make an 'informed' and independent decision about whether or not they would like to participate. If this applies to you and the person you care for, then we would like to ask you to decide whether or not you think that it is in your child's best interests for them to participate in the study and whether you would like to provide your consent to participation on their behalf. If you would like your child/person you care for to participate in this study, please check the box to complete the consent form.

Appendix I1: Consent Forms from Online Survey: Individuals able to consent

[redacted] [redacted]

Consent Form: For individuals who are able to provide consent to participate in the study

Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders

Study Director: [redacted]

SECTION 1: Please complete this section if you are a person with Sotos syndrome

1. Has somebody else explained the project to you or have you read the information? YES□ NO□
2. Do you understand what the project is about? YES□ NO□
3. Have you asked all of the questions you want? YES□ NO□
4. Have you had your questions answered in a way you understand? YES□ NO□
5. Do you understand it is OK to stop taking part at any time? YES□ NO□
6. Are you are happy to take part? YES□ NO□

If you checked no to any answers or you don't want to take part, don't type your name!

If you do want to take part, you can type your name below

You can also choose if you want to say 'yes' to these:

7. If your Dr asks to see your results from this project it is OK for us to share this with them? YES□ NO□
8. Are you are happy for us to contact you again in the future YES□ NO□
9. Are you happy to provide a saliva sample that we will use to understand more about the cause of your syndrome/disability? YES□ NO□

Your name: _____Date: _____

The person who explained this project to you needs to sign too. If you are not aged 16 or above, this should be your parent/guardian.

Print name: _____

Date: _____

<u>SECTION 2:</u> Please complete this section if you are a parent/carer/guardian of a person with Sotos syndrome who has provided their consent to participate in the study.

	Please check box…
1. I confirm that I have read and understood the information sheet dated for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation and that of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reason, without my or that of my child's/person I care for's medical care or legal rights being affected.	☐
3. I understand that relevant sections of my child's/person I care for's GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the [redacted] research team at the [redacted], where it is relevant to this research project. I give permission for these individuals to have access to these records.	☐
4. I agree to my child's/person I care for's GP being informed of my participation and that of my child/person I care for's in the study, where access to my child's/person I care for's medical records is required.	☐
5. I agree to take part in the above study.	☐

Optional clauses: The statements below are <u>optional</u>:

1. I agree to the [redacted] research team sharing my research data with any professionals or clinicians working with me and the person I care for should they request to see them.	☐
2. I agree to my child/person I care for providing a saliva sample that will be used for analysis of genetic information and I understand that the information found will not be fed back to me routinely.	☐

Print Name: _____ Telephone number:_____

Address:_____
Email: _____
Relationship to participant: _____Date: _____

Appendix I2: Consent Forms from Online Survey: Individuals over age of 16 unable to consent

[redacted] [redacted]

Consent Form: For individuals over the age of 16 who are not able to provide consent.

Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders

Study Director: [redacted]

Please read the following statements:

Please check box…

1. I (your name)_____have been consulted about (name of participant)_____'s participation in the above research project. I have had the opportunity to ask questions about the study and understand what is involved. ☐
2. In my opinion he/she would have no objection to taking part in the above study. ☐
3. I understand that I can request he/she is withdrawn from the study at any time without giving any reason and without his/her care or legal rights being affected. ☐
4. I understand that relevant sections of his/her GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the [redacted] research team at the [redacted], where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐
5. I agree to his/her GP being informed of their participation in the study, where access to medical records is required. ☐
6. I agree to take part in the above study. ☐

Optional clauses: The statements below are optional:

3. I agree to the [redacted] research team sharing his/her research data with any professionals or clinicians working with them should they request to see them. ☐
4. I agree to my child/person I care for providing a saliva sample that will be used for analysis of genetic information and I understand that the information found will not be fed back to me routinely. ☐

Print Name: _____ Telephone number: _____

Address: _____Email: _____

Relationship to participant: _____Date: _____

Appendix I3: Consent Forms from Online Survey: Individuals under age of 16 unable to consent

[redacted] [redacted]

Consent Form: For children under the age of 16 who are not able to provide consent.

Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders

Study Director: [redacted]

Please complete this section if you are a parent/ guardian of a child (under 16 years) with Sotos syndrome who is not able to provide consent.

Please check box…

1. I confirm that I have read and understood the information sheet dated for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation and that of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reason, without my or that of my child's/person I care for's medical care or legal rights being affected. ☐
3. I understand that relevant sections of my child's/person I care for's GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the [redacted] research team at the [redacted], where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐
4. I agree to my child's/person I care for's GP being informed of my participation and that of my child/person I care for's in the study, where access to my child's/person I care for's medical records is required. ☐
5. I agree to take part in the above study. ☐

Optional clauses: The statements below are optional:

I agree to the [redacted] research team sharing my research data with any professionals or clinicians working with me and the person I care for should they request to see them. ☐

I agree to my child/person I care for providing a saliva sample that will be used for analysis of genetic information and I understand that the information found will not be fed back to me routinely. ☐

Print Name: _____ Name of person you care for:_____

Address: _____Email: _____

Telephone number: _____ Relationship to participant: _____Date: _____

Appendix J: Demographics Questionnaire

BACKGROUND INFORMATION

Please tick or write your response to these questions concerning background details:

Please answer the following about the person you care for:

1. **Is the person you care for verbal?** (i.e. more than 30 signs/words in their vocabulary)
   Yes/No (delete as appropriate)

2. **Is the person you care for able to walk unaided?**
   Yes/No (delete as appropriate)

In the information sheet and consent form we informed you that we may need to contact your child's/person you care for's GP in order to clarify any information regarding your child's health and diagnostic status (see consent form and information sheet for more information). If you have already indicated on the consent form that you are happy for us to do this, please complete the relevant details below:

3. **Name of your child's/person you care for's**

   GP_____

   GP Address_____

   GP Telephone number_____

The following questions ask for background information about you and your family. Please tick the appropriate boxes or write in the spaces provided.

1. Are you male or female? Male ☐ Female ☐

2. What was your age in years on your last birthday? _____years

3. Please tick the highest level of your educational qualifications.

No formal educational qualifications	☐
Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC First Diploma	☐
5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent	☐
3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent	☐
Polytechnic/University degree, NVQ 4, or equivalent	☐
Masters/Doctoral degree, NVQ 5, or equivalent	☐

4. What is your relationship to your child with a genetic syndrome (e.g. mother, father, stepmother, grandmother, adoptive parent)? _____

5. In total how many people currently live in your home? _____ Adults _____ Children

6. Does your child with a genetic syndrome normally live with you? Yes ☐ **No** ☐

If no, then where do they live? _____

7. What is your current marital status?

Married, and living with spouse..... ☐

Living with partner..... ☐

Divorced/Separated/Widowed/Single and NOT living with a partner..... ☐

If living with partner/spouse, please answer the following questions, if not, please go to question 12.

8. Is your partner male or female? Male ☐ Female ☐

9. What was their age in years on their last birthday? _____ years

10. Please tick the highest level of your partner/spouse's educational qualifications.

No formal educational qualifications ☐

Fewer than 5 GCSE or O Level (grades A-C), NVQ 1, or BTEC First Diploma ☐

5 or more GCSE or O Level (grades A-C), NVQ 2, or equivalent ☐

3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent ☐

Polytechnic/University degree, NVQ 4, or equivalent ☐

Masters/Doctoral degree, NVQ 5, or equivalent ☐

11. What is your partner/spouse's relationship to your child with a genetic syndrome (e.g., mother, father, stepmother, adoptive parent)? _____

12. Recent data from research with families of children with special needs has shown that a family's financial resources are important in understanding family member's views and experiences. With this in mind, we would be very grateful if you could answer the additional question below. We are not interested in exactly what your family income is, but we would like to be able to look at whether those with high versus lower levels of financial resources have different experiences.

What is your current total annual family income? Please include a rough estimate of total salaries and other income (including benefits) before tax and national insurance/pensions.

Please tick one box only:

Less than £15,000 ☐

£15,001 to £25,000 ☐

£25,001 to £35,000 ☐

£35,001 to £45,000 ☐

£45,001 to £55,000 ☐

£55,001 to £65,000 ☐

£65,001 or more ☐

Appendix K: The Wessex Scale

WESSEX Scale

These items refer to the person you care for. For each question (A, B, C, D etc …), please enter the appropriate code in each box.

(Frequently = more than once a week)

A) Wetting (nights)	**1** = frequently	**2** = occasionally	**3** = never	☐
B) Soiling (nights)	**1** = frequently	**2** = occasionally	**3** = never	☐
C) Wetting (days)	**1** = frequently	**2** = occasionally	**3** = never	☐
D) Soiling (days)	**1** = frequently	**2** = occasionally	**3** = never	☐
E) Walk with help	**1** = not at all	**2** = not up stairs	**3** = up stairs and elsewhere	☐

(note: if this person walks *by himself* upstairs and elsewhere, please also code '3' for 'walk with help')

F) Walk by himself	**1** = not at all	**2** = not up stairs	**3** = up stairs and elsewhere	☐
G) Feed himself	**1** = not at all	**2** = with help	**3** = without help	☐
H) Wash himself	**1** = not at all	**2** = with help	**3** = without help	☐
I) Dress himself	**1** = not at all	**2** = with help	**3** = without help	☐

J) Vision	**1** = blind or almost	**2** = poor	**3** = normal	☐
K) Hearing	**1** = deaf or almost	**2** = poor	**3** = normal	☐

L) Speech **1** = never a word **2** = odd words only **3** = sentences and normal **4** = can talk but doesn't ☐

If this person talks in sentences, is his/her speech:

1 = Difficult to understand even by acquaintances, impossible for strangers?

2 = Easily understood for acquaintances, difficult for strangers?

3 = Clear enough to be understood by anyone? ☐

M) Reads	**1** = nothing	**2** = a little	**3** = newspapers and/or books	☐
N) Writes	**1** = nothing	**2** = a little	**3** = own correspondence	☐
O) Counts	**1** = nothing	**2** = a little	**3** = understands money values	☐

Appendix L: The Activity Questionnaire

THE ACTIVITY QUESTIONNAIRE

Instructions:

- Please read each item carefully and circle the appropriate number on the scale, for the person you care for.
- Please ensure that you indicate a response for every item. If the particular behaviour does not apply, e.g., if the person is not verbal or not mobile, please circle 0 on the scale.

	Never/ almost never	Some of the time	Half of the time	A lot of the time	Always/ almost all the time
1. **Does the person wriggle or squirm about when seated or lying down?**	**0**	**1**	**2**	**3**	**4**
2. Does the person fidget or play with their hands and/or feet when seated or lying down?	**0**	**1**	**2**	**3**	**4**
3. **Does the person find it difficult holding still?**	**0**	**1**	**2**	**3**	**4**
4. **Does the person find it difficult to remain in their seat even when in situations where it would be expected?**	**0**	**1**	**2**	**3**	**4**
5. **Does the person prefer to be moving around or becomes**	**0**	**1**	**2**	**3**	**4**
6. **When the person is involved in a leisure activity (e.g. watching TV, playing a game etc.) do they make a lot of noise?**	**0**	**1**	**2**	**3**	**4**
7. **When the person is involved in an activity, are they boisterous and/or rough?**	**0**	**1**	**2**	**3**	**4**
8. **Does the person act as if they are "driven by a motor" (i.e. often very active)?**	**0**	**1**	**2**	**3**	**4**
9. **Does the person seem like they need very little rest to recharge their battery?**	**0**	**1**	**2**	**3**	**4**
10. **Does the person often talk excessively?**	**0**	**1**	**2**	**3**	**4**
11. **Does the person's behaviour seem difficult to manage/contain whilst out and about (e.g. in town, in supermarkets etc.)?**	**0**	**1**	**2**	**3**	**4**
12. **Do you feel that you need to "keep an eye" on the person at all times?**	**0**	**1**	**2**	**3**	**4**
13. **Does the person you care for seem to act/do things without stopping to think first?**	**0**	**1**	**2**	**3**	**4**
14. **Does the person blurt out answers before questions have been completed?**	**0**	**1**	**2**	**3**	**4**
15. **Does the person start to respond to instructions before they have been fully given or without seeming to understand them?**	**0**	**1**	**2**	**3**	**4**
16. **Does the person want things immediately?**	**0**	**1**	**2**	**3**	**4**
17. **Does the person find it difficult to wait?**	**0**	**1**	**2**	**3**	**4**
18. **Does the person disturb others because they have difficulty waiting for things or waiting their turn?**	**0**	**1**	**2**	**3**	**4**

Appendix M: The Repetitive Behaviour Questionnaire

THE RBQ

INSTRUCTIONS

1. The questionnaire asks about 19 different behaviours.
2. Each behaviour is accompanied by a brief definition and examples. The examples given for each behaviour are not necessarily a complete list but may help you to understand the definitions more fully.
3. Please read the definitions and examples carefully and circle the appropriate number on the scale to indicate how frequently the person you care for has engaged in each of the behaviours **within the last month**.
4. If a particular behaviour does not apply to the person you care for because they are not mobile or verbal please circle the number 0 on the scale

	Never	**Once a month**	**Once a week**	**Once a day**	**More than once a day**
1. Object stereotypy: repetitive, seemingly purposeless movement of objects in an unusual way *E.g. twirling or twiddling objects, twisting or shaking objects, banging or slapping objects.*	**0**	**1**	**2**	**3**	**4**
2. Body stereotypy: repetitive, seemingly purposeless movement of whole body or part of body (other than hands) in an unusual way. *E.g. body rocking, or swaying ,or spinning, bouncing, head shaking, body posturing..* Does not include self-injurious behaviour.	**0**	**1**	**2**	**3**	**4**
3. Hand stereotypy: repetitive, seemingly purposeless movement of hands in an unusual way. *E.g. finger twiddling, hand flapping, wigging or flicking fingers, hand posturing.* Does not include self-injurious behaviour.	**0**	**1**	**2**	**3**	**4**
4. Cleaning: Excessive cleaning, washing or polishing of objects or parts of the body. E*.g. polishes windows and surfaces excessively, washes hands and face excessively,*	**0**	**1**	**2**	**3**	**4**
5. Tidying up: Tidying away any objects that have been left out. This may occur in situations when it is inappropriate to put the objects away. Objects may be put away into inappropriate places. *E.g. putting cutlery left out for dinner in the bin, removes all objects from surfaces.*	**0**	**1**	**2**	**3**	**4**
6. Hoarding: Collecting, storing or hiding objects to excess, including rubbish, bits of paper, and pieces of string or any other unusual items.	**0**	**1**	**2**	**3**	**4**
7. Organising objects: Organising objects into categories according to various characteristics such as colour, size, or function. *E.g. ordering magazines according to size, ordering toy cars according to colour, ordering books according to topic.*	**0**	**1**	**2**	**3**	**4**
8. Attachment to particular people: Continually asking to see, speak or contact a particular 'favourite' person. *E.g. continually asks to see or speak to particular friend, carer, babysitter or schoolteacher.*	**0**	**1**	**2**	**3**	**4**

	Never	Once a month	Once a week	Once a day	More than once a day
9. Repetitive questions: Asking specific questions over and over. *E.g. always asking people what their favourite colour is, asking who is taking them to school the next day over and over*	**0**	**1**	**2**	**3**	**4**
10. Attachment to objects: Strong preference for a particular object to be present at all times. *E.g. Carrying a particular piece of string everywhere, taking a particular red toy car everywhere, attachment to soft toy or particular blanket.*	**0**	**1**	**2**	**3**	**4**
11. Repetitive phrases/signing: Repeating particular sounds, phrases or signs that are unrelated to the situation over and over. *E.g. repeatedly signing the word 'telephone'.*	**0**	**1**	**2**	**3**	**4**
12. Rituals: carrying out a sequence of unusual or bizarre actions before, during or after a task. The sequence will always be carried out when performing this task and will always occur in the same way. *E.g. turning round three times before sitting down, turning lights on and off twice before leaving a room, tapping door frame twice when passing through it.*	**0**	**1**	**2**	**3**	**4**
13. Restricted conversation: Repeatedly talks about specific, unusual topics in great detail. *E.g. conversation restricted to: trains, buses, dinosaurs, particular film, country, or sport.*	**0**	**1**	**2**	**3**	**4**
14. Echolalia: Repetition of speech that has either just been heard or has been heard more than a minute earlier. *E.g.: Mum:' Jack don't do that' Jack: 'Jack don't do that'.*	**0**	**1**	**2**	**3**	**4**
15. Preference for routine: Insist on having the same household, school or work schedule everyday. *E.g. likes to have the same activities on the same day at the same time each week, prefers to eat lunch at exactly the same time every day, wearing the same jumper everyday.*	**0**	**1**	**2**	**3**	**4**
16. Lining up or arranging objects*: Arrangement of objects into lines or patterns E.g. placing toy cars in a symmetrical pattern, precisely lining up story books,*	**0**	**1**	**2**	**3**	**4**
17. Just right behaviour: Strong insistence that objects, furniture and toys always remain in the same place. *E.g. all chairs, pictures and toys have a very specific place that cannot be changed.*	**0**	**1**	**2**	**3**	**4**
18. Completing behaviour: Insists on having objects or activities 'complete' or 'whole' *E.g. Must have doors open or closed not in between, story must be read from beginning to end, not left halfway through.*	**0**	**1**	**2**	**3**	**4**
19. Spotless behaviour: Removing small, almost unnoticeable pieces of lint, fluff, crumbs or dirt from surfaces, clothes and objects. *E.g. Picking fluff off a jumper, removing crumbs from the kitchen table.*	**0**	**1**	**2**	**3**	**4**

Appendix N: Social Communication Questionnaire

SOCIAL COMMUNICATION QUESTIONNAIRE © Rutter *et al.* 2003

Please circle 'yes' if <u>any</u> one of the following behaviours is present. Although you may be uncertain about whether some behaviours are present or not, please do answer 'yes' or 'no' to every question on the basis of what you think.

1. Is she/he now able to talk using short phrases or sentences? If no, skip to question 8.	**Yes** **No**
2. Do you have a to and fro "conversation" with her/him that involves taking turns or building on what you have said?	**Yes** **No**
3. Does she/he ever use odd phrases or say the same thing over and over in almost exactly the same way (either phrases she/he has heard other people use or ones that she/he makes up)?	**Yes** **No**
4. Does she/he ever use socially inappropriate questions or statements? For example, does she/he ever regularly ask personal questions or make personal comments at awkward times?	**Yes** **No**
5. Does she/he ever get her/his pronouns mixed up (e.g. saying *you* or *she/he* instead of *I*)	**Yes** **No**
6. Does she/he ever use words that she/he seems to have invented or made up her/himself; put things in odd, indirect ways; or use metaphorical ways of saying things (e.g. saying *hot rain* for *steam*)?	**Yes** **No**
7. Does she/he ever say the same thing over and over in exactly the same way, or insist that you say the same thing over and over again?	**Yes** **No**
8. Does she/he ever have things that she/he seems to have to do in a very particular way or order, or rituals that she/he insists that you go through?	**Yes** **No**
9. Does her/his facial expression usually seem appropriate to the particular situation, so far as you can tell?	**Yes** **No**
10. Does she/he ever use your hand like a tool, or as if it were part of her/his own body (e.g. pointing with your finger, putting your hand on a doorknob to get you to open the door)?	**Yes** **No**
11. Does she/he ever have any interests that preoccupy her/him and might seem odd to other people (e.g. traffic lights, drainpipes or timetables)?	**Yes** **No**
12. Does she/he ever seem to be more interested in parts of a toy or an object (e.g. spinning the wheels of a car), rather than using the object as it was intended?	**Yes** **No**
13. Does she/he ever have any special interests that are *unusual* in their intensity but otherwise appropriate for her/his age and peer group (e.g. trains, or dinosaurs)?	**Yes** **No**
14. Does she/he ever seem to be *unusually* interested in the sight, feel, sound, taste or smell of things or people?	**Yes** **No**

15. Does she/he ever have any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes?	**Yes** **No**
16. Does she/he ever have any complicated movements of her/his whole body, such as spinning or repeatedly bouncing up and down?	**Yes** **No**
17. Does she/he ever injure her/himself deliberately, such as by biting her/his arm or banging her/his head?	**Yes** **No**
18. Does she/he ever have any objects (*other* than a soft toy or comfort blanket) that she/he *has* to carry around?	**Yes** **No**
19. Does she/he have any particular friends or a best friend?	**Yes** **No**
20. Does she/he ever talk with you just to be friendly (rather than to get something)?	**Yes** **No**
21. Does she/he ever spontaneously copy you (or other people) or what you are doing (such as vacuuming, gardening or mending things)?	**Yes** **No**
22. Does she/he ever spontaneously point at things around her/him just to show you things (not because she/he wants them)?	**Yes** **No**
23. Does she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wants?	**Yes** **No**
24. Does she/he nod her/his head to indicate *yes*?	**Yes** **No**
25. Does she/he shake her/his head to indicate *no*?	**Yes** **No**
26. Does she/he usually look at you directly in the face when doing things with you or talking with you?	**Yes** **No**
27. Does she/he smile back if someone smiles at her/him?	**Yes** **No**
28. Does she/he ever show you things that interest her/him to engage your attention?	**Yes** **No**
29. Does she/he ever offer to share things other than food with you?	**Yes** **No**
30. Does she/he ever seem to want you to join in her/his enjoyment of something?	**Yes** **No**
31. Does she/he ever try to comfort you if you are sad or hurt?	**Yes** **No**
32. If she/he wants something or wants help, does she/he look at you and use gestures with sounds or words to get your attention?	**Yes** **No**
33. Does she/he show a normal range of facial expressions?	**Yes** **No**

34. Does she/he ever spontaneously join in and try to copy the actions in social games, such as The Mulberry Bush or London Bridge is Falling Down?	**Yes** **No**
35. Does she/he play any pretend or make-believe games?	**Yes** **No**
36. Does she/he seem interested in other children whom she/he does not know?	**Yes** **No**
37. Does she/he respond positively when another child approaches her/him?	**Yes** **No**
38. If you come into a room and start talking to her/him without calling her/his name, does she/he usually look up and pay attention to you?	**Yes** **No**
39. Does she/he ever play imaginative games with another child in such a way that you can tell that each child understands what the other is pretending?	**Yes** **No**
40. Does she/he play cooperatively in games that need some form of joining in with a group of other children, such as hide-and-seek or ball games?	**Yes** **No**

Appendix O: The Sociability Questionnaire for People with Intellectual Disability

THE SOCIABILITY QUESTIONNAIRE FOR PEOPLE WITH INTELLECTUAL DISABILITIES (SQID)

Instructions:

This questionnaire asks you how the person you care for typically behaved in social situations over the last two months. Each situation will involve one of the following:

1. *The person's main caregiver*: Someone that provides the main support and care for the person, e.g. a parent or carer.

2. *A familiar adult or someone familiar of the same age*: Someone that knows the person relatively well but does *not* provide the main care for the person, e.g. a relative *not* in the immediate family, a friend of the family, a support worker at school / college, a friend at school / college etc.

3. *An adult or someone of the same age that the person does not know*: Someone the person has *never* met before, e.g. a stranger, a new teacher, a new support worker at school / college, someone new of the same age at school / college etc.

The person may appear 'sociable', 'shy' or somewhere in between in the situations given below.

- If the person is 'sociable' (s)he may show one or more of the following behaviours: looks pleased; starts to speak or sign to others; turns face and / or body towards others; or tries to gain other people's attention in someway.
- If the person is 'shy' (s)he may show one or more of the following behaviours: looks a little sad or distressed; reluctant to speak or sign to others; turns head and / or body away from others; tries to avoid or remove himself / herself from situations when other people are present.

Read each question and circle the response that best describes the behaviour of the person in the situation described.

For example, for question 4 if you think that when the person is spending time with a familiar adult (s)he would be 'very sociable' then your answer would look like this:-

4. (S)he is spending time with a familiar adult? 1 2 3 4 5 6 (7)

How would the person you care for appear if…	**Very shy**	**Moderately shy**	**A little shy**	**Neither**	**A little sociable**	**Moderately sociable**	**Very sociable**
1. Her / his main caregiver walks up to her / him?	**1**	**2**	**3**	**4**	**5**	**6**	**7**
2. (S)he is spending time with an adult (s)he does *not* know? ……...	**1**	**2**	**3**	**4**	**5**	**6**	**7**
3. Someone (s)he does *not* know that is her / his own age walks up to her /him? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
4. (S)he is spending time with a familiar adult? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
5. (S)he is the focus of attention in a group of adults (s)he knows? ……..	**1**	**2**	**3**	**4**	**5**	**6**	**7**
6. (S)he is spending time with someone (s)he does *not* know that her / his own age? ……..	**1**	**2**	**3**	**4**	**5**	**6**	**7**
7. Someone familiar that is her / his own age walks up to her /him? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
8. (S)he has just been separated from her / his main caregiver to be with an adult (s)he does *not* know? …….....	**1**	**2**	**3**	**4**	**5**	**6**	**7**
9. An adult (s)he does *not* know walks up to her / him? ……	**1**	**2**	**3**	**4**	**5**	**6**	**7**
10. (S)he is the focus of attention in a group of people her / his own age that (s)he does *not* know? ……...	**1**	**2**	**3**	**4**	**5**	**6**	**7**
11. (S)he is spending time with someone familiar that is her / his own age? ……	**1**	**2**	**3**	**4**	**5**	**6**	**7**
12. (S)he is the focus of attention in a group of people her / his own age that (s)he knows? …	**1**	**2**	**3**	**4**	**5**	**6**	**7**

How would the person you care for appear if…	**Very shy**	**Moderately shy**	**A little shy**	**Neither**	**A little sociable**	**Moderately sociable**	**Very sociable**
13. (S)he is with her / his main caregiver and then someone her / his own age that (s)he does *not* know starts to talk to her / him? ……....	**1**	**2**	**3**	**4**	**5**	**6**	**7**
14. A familiar adult walks up to her / him? ……....	**1**	**2**	**3**	**4**	**5**	**6**	**7**
15. (S)he is with her / his main caregiver and then an adult (s)he does *not* know starts to talk to her / him? ……..	**1**	**2**	**3**	**4**	**5**	**6**	**7**
16. (S)he is spending time with her / his main caregiver? ……..	**1**	**2**	**3**	**4**	**5**	**6**	**7**
17. (S)he is the focus of attention in a group of adults (s)he does *not* know? ……....	**1**	**2**	**3**	**4**	**5**	**6**	**7**

	Never or very rarely	**Rarely**	**Sometimes**	**About half the time**	**Often**	**Very often**	**Nearly Always**
18. When there are only familiar people around, how often does (s)he try to make contact with them in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)? …….	**1**	**2**	**3**	**4**	**5**	**6**	**7**
19. When familiar people and people are around who (s)he does *not* know, how often does (s)he try to make contact with the people (s)he does *not* know in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)? ……	**1**	**2**	**3**	**4**	**5**	**6**	**7**
20. When familiar people and people are around who (s)he does *not* know, how often does (s)he try to make contact with the familiar people in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)? ……	**1**	**2**	**3**	**4**	**5**	**6**	**7**
21. When there are only people around who (s)he does *not* know, how often does (s)he try to make contact with them in any way (by talking, signing, vocalising, using gestures, moving towards them in any way etc.)? ……..	**1**	**2**	**3**	**4**	**5**	**6**	**7**

	YES	**NO**
22. Does the person you care for speak or sign **more** than 30 words?	☐	☐

If you answered **'yes'** to this question, please complete the rest of the questionnaire. If you answered **'no'**, please complete the box at the end of the questionnaire if there is anything else you think we should know.

23. Does the person speak *less* than (s)he used to?	☐	☐
24. Does the person *only* speak or sign in some settings and not others?	☐	☐

If 'yes' please describe

……
……

25. Does the person *only* speak or sign to some people and not others?	☐	☐

If 'yes' please describe

……
……

Is there anything else you want to tell us about how the person you care for appears in social situations with other people (s)he knows or doesn't know, when separated from you, in a group setting or is the centre of attention in a group of people?

……
……
……

Please check your answers and go on to the next questionnaire.

Appendix P: The Challenging Behaviour Questionnaire

THE CBQ

1) Has the person shown self-injurious behaviour in the last month? (e.g. head banging, head-punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing).

Yes ☐ No ☐

If the behaviour has not occurred, please go to question 6.
If the behaviour occurred in the past month please answer questions 2 to 5:

2) Place a tick next to the item for any of the following list of behaviours which the person displays in a repetitive manner (repeats the same movement/ behaviour twice or more in succession):

Hits self with body part (e.g. slaps head or face)…… ☐
Hits self against surface or object (e.g. bangs head on floor or table)…… ☐
Hits self with object…… ☐
Bites self (e.g. bites hand on wrist or arm)……... ☐
Pulls (e.g. pulls hair or skin)……..... ☐
Rubs or scratches self (e.g. rub marks on arm or leg)……. ☐
Inserts finger or objects (e.g. eye poking)……..... ☐
Other form of self-injury, please specify:…… ☐

3) In the last month, for how long did the **longest** episode or burst of his behaviour last? *(Please circle one number)*

1	2	3	4	5
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

4) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	1	2	3	4
Never	At least once a month	At least once a week	At least once a day	At least once an hour

5) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	2	3	4	5
By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

6) Has the person shown physical aggression in the last month? (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing).

Yes ☐ No ☐

7) Has the person shown disruption and destruction of property or the environment in the last month? (e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal).

Yes ☐ No ☐

8) Has the person shown stereotyped behaviours in the last month? (e.g. rocking twiddling objects, patting or tapping part of the body, constant hand movements, eye pressing).

Yes ☐ No ☐

Appendix Q: The Mood, Interest and Pleasure Questionnaire-Short Version

The Mood, Interest And Pleasure Questionnaire –
Short Form (MIPQ-S)

Instructions for completing the MIPQ-S

This questionnaire contains 12 questions – you should complete all 12 questions. Each question will ask for your opinion about particular behaviours, which you have observed in the last 2 weeks. For every question you should circle the most appropriate response e.g.

6) In the last two weeks, how interested did the person appear to be in his/her surroundings?

interested all of the time	*interested most of the time*	*interested about half of the time*	*interested some of the time*	*never interested*

The Mood, Interest and Pleasure Questionnaire - Short Form

1) In the last two weeks, did the person seem…

sad all of the time	sad most of the time	sad about half of the time	sad some of the time	never sad

Please comment if anything has happened in the last two weeks which you feel might explain sadness if it has been observed (e.g. a bereavement):

2) In the last two weeks, how often did you hear positive vocalizations* when the person was engaged in activities*?

all of the Time	most of the the time	about half of the time	some of the time	never

*positive vocalizations: e.g. laughing, giggling, "excited sounds" etc.
*engaged in activities: i.e. when someone is actively involved in any activity such as a mealtime, a social interaction, a self-care task or social outing etc.

3) In the last two weeks, do you think the facial expression of the person looked "flat"*…

all of the time	most of the the time	about half of the time	some of the time	never

*flat expression: expression seems lifeless; lacks emotional expression; seems unresponsive.

4) In the last two weeks, would you say the person…

cried every Day	cried nearly every day	cried 3-4 times each week	cried once or twice each week	cried less than once each week

5) In the last two weeks, how interested did the person appear to be in his/her surroundings?

interested all	interested most	interested about	interested some	never

of the time	of the time	half of the time	of the time	interested

6) In the last two weeks, did the person seem to have been enjoying life…

all of the time	most of the the time	about half of the time	some of the time	never

Please comment if there are any reasons why this person might not have been enjoying him/herself e.g. illness, being in pain, experiencing a loss etc.:

7) In the last two weeks, would you say the person smiled…

at least once every day	at least once nearly every day	3-4 times each week	once or twice each week	less than once each week

8) In the last two weeks, how disinterested did the person seem to be in his/her surroundings?

disinterested all of the time	disinterested most of the time	disinterested about half of the time	disinterested some of the time	never disinterested

9) In the last two weeks, when the person was engaged in activities*, to what extent did his/her facial expressions* suggest that s/he was interested in the activity?

interested all of the time	interested most of the time	interested about half of the time	interested some of the time	never interested

*engaged in activities: i.e. when someone is actively involved in any activity such as a mealtime, social interaction, self-care task or social outing etc.
*facial expressions: interest might be indicated by the degree to which the person's gaze is being directed at the person/things involved in an activity.

10) In the last two weeks, would you say that the person…

laughed every day	laughed nearly every day	laughed 3-4 times each week	laughed once or twice each week	laughed less than once each week

11) In the last two weeks, how often did you see gestures which appeared to demonstrate enjoyment* when the person was engaged in activities*?

all of the time	most of the the time	about half of the time	some of the time	never

*gestures which appear to demonstrate enjoyment: e.g. clapping, waving hands in excitement etc.
*engaged in activities: i.e. when someone is actively involved in any activity such as a meal time, social interaction, self-care task or social outing etc.

12) In the last two weeks, did the person's vocalizations* sound distressed…

all of the time	most of the the time	about half of the time	some of the time	never

*vocalizations: any words, noises or utterances.

Appendix R: Sensory Experiences Questionnaire – Short Form

SENSORY EXPERIENCES QUESTIONNAIRE (SEQ)
Short Form

(Note: formerly known as the Sensory Supplement Questionnaire - SSQ)

Version 2.1 ©1999 Grace T. Baranek, Ph.D., OTR/L

Child's ID #: _____ **Date:** _____ **Child's Birthdate:** _____ **Gender: F ☐ M ☐**

Person completing form (check one):

Mother ☐ Father ☐ Both Parents ☐ Teacher ☐ Other ☐ (describe:_____)

Directions

The following are some brief questions about how your child uses his/her senses (for example hearing, vision, touch, etc.) to experience the world. No two children are alike. This questionnaire asks about behaviors that make your child unique. Consider your child's usual responses to these situations or activities. The questions ask **how often your child responds or behaves in a certain way.** Check the box that fits best (almost never, once in a while, sometimes, frequently, almost always). Answer all questions completely.

For more information about the SEQ contact:
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(Research version: 04/18/2013)

ID #: _____ **Date:** _____ 1

Experiences with Sound:

Does your child react sensitively or startle easily to unexpected or loud sounds? (For example: covers ears when hearing a vacuum, baby cry, door close, etc.)	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					1-A-R-N
Does your child enjoy listening to music?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					2-D-Y
Does your child ignore you when you call his/her name?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					3-A-O-S
Does your child seem to ignore or tune-out loud noises? (For example: no reaction when alarms go off, vacuum turns on or object falls to the floor.)	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					4-A-O-N
Does your child notice sounds in the environment (such as planes, trains, faucets dripping, lights buzzing, etc.) before other people do?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					5-A-R-N
Does your child show distress (startles, covers ears, etc.) during loud conversations or singing?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					6-A-R-S

Experiences with Sight:

Does your child enjoy looking at picture books?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					7-D-Y
Is your child disturbed by too much light inside or brightness outside?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					8-V-R-N
Does your child stare at lights or objects that spin or move?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					9-V-SS-N
Is your child slow to notice new objects or toys in the room, or slow to look at objects that are placed or held near him/her?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					10-V-O-X
Does your child avoid looking at your face during social games/play?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					11-V-R-S
Does your child seem to ignore (doesn't notice) when someone new or different enters the room?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					12-V-O-S
Does your child enjoy watching children's videos or TV programs?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					13-D-Y

ID #: _____ **Date:** _____ 2

Experiences with Touch:

Does your child dislike cuddling or being held?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					14-T-R-S
Does your child show distress during grooming? (For example: cries or fusses during face washing, hair combing, fingernail cutting, or teeth brushing)?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					15-T-R-N
Does your child avoid touching certain textures (such as fuzzy or squishy toys) or playing with messy materials (such as sand, lotion)?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					16-T-R-N
Does your child react negatively or pull away when touched by a person? (For example: pulls away when head is patted.)	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					17-T-R-S
Does your child have trouble adjusting to the water temperature during bath time or does he/she dislike being in water?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					18-T-R-N
Does your child seem slow to react to pain? (For example: he/she isn't bothered by bumps scrapes, cuts, or falls.)	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					19-T-O-N
Does your child dislike being tickled?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					20-T-R-S
Does your child ignore you (doesn't notice) when you tap him/her on the shoulder for attention?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					21-T-O-S

Experiences with Taste or Smell:

Does your child refuse to try new foods or avoid certain tastes, smells, or textures (consistencies) of food?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					22-G-R-N
Does your child smell objects or toys during play or other activities?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					23-G-SS-N
Does your child seem interested in the way people smell? (For example: smells hair, breath.)	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					24-G-SS-S
Does your child put objects, toys or other non-food items in his/her mouth to lick, suck, or explore?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					25-G-SS-N

ID #: _____ **Date:** _____ 3

Experiences with Movement:

Does your child enjoy riding in a car?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					26-D-Y
Does your child like to jump up/down, rock back/forth, or spin in circles?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					27-P-SS-N
Does your child seek out physical rough-housing play? (For example: craves being tossed in the air or spun around.)	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					28-P-SS-S
Does your child seem uneasy or become dizzy when moving on a swing or rocking chair, for example?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					29-P-R-N
Does your child flap his/her arms or hands repeatedly, particularly when excited?	*Almost Never* ☐	*Once in a While* ☐	*Sometimes* ☐	*Frequently* ☐	*Almost Always* ☐
					30-P-SS-N

List other comments you would like to make about your child's preferred experiences or avoidances/sensitivities to sound, sight, touch, smell, taste, or movement.

_____

_____

_____

35-X

ID #: _____ **Date:** _____ 4

SEQ Addendum for Fascinations:

How often is your child extremely fascinated with:

A. Sounds

Almost Never	*Once in a While*	*Sometimes*	*Frequently*	*Almost Always*	
☐	☐	☐	☐	☐	36a-A-SS-N

B. Lights

Almost Never	*Once in a While*	*Sometimes*	*Frequently*	*Almost Always*	
☐	☐	☐	☐	☐	36b-V-SS-N

C. Smells

Almost Never	*Once in a While*	*Sometimes*	*Frequently*	*Almost Always*	
☐	☐	☐	☐	☐	36c-G-SS-N

D. Tastes

Almost Never	*Once in a While*	*Sometimes*	*Frequently*	*Almost Always*	
☐	☐	☐	☐	☐	36d-G-SS-N

E. Textures

Almost Never	*Once in a While*	*Sometimes*	*Frequently*	*Almost Always*	
☐	☐	☐	☐	☐	36e-T-SS-N

F. Touch

Almost Never	*Once in a While*	*Sometimes*	*Frequently*	*Almost Always*	
☐	☐	☐	☐	☐	36f-T-SS-N

Does your child "seek" or "crave" particular sensory experiences?
If so please describe all fascinations/cravings.

_____

_____

_____

Appendix S: The Anxiety, Depression and Mood Scale

ANXIETY DEPRESSION AND MOOD SCALE

(ADAMS)

Date: _____

Background Information of Individual being Rated

Gender: □ Male □ Female **Age:**_____

Ethnicity: □ African-American □ Asian/Pacific Islander □ Hispanic American
□ American Indian/Eskimo □ Caucasian □ Other _____

Level of intellectual disability: □ Borderline □ Moderate □ Profound
□ Mild □ Severe □ Don't Know

Living situation: □ Own home without supports □ Small group home (<7 residents)
□ Own home with supports □ Midsize group home (7-15 residents)
□ Home with parents □ Nursing home
□ Staffed apartment □ Large facility (state school/ID centre >15 residents)
□ Foster care/live-in staff □ Other residential facility_____

Disabilities: □ Speech/language impairment □ Psychiatric disorder □ Physical disability
□ Deafness/hearing impairment □ Chronic health condition □ Autism
□ Brain/neurological impairment □ Legal blindness □ Learning disability
□ Other _____

Information of Individual Completing Form

Your Relationship with individual: □ Direct Care Staff □ Teacher □ Work Supervisor
□ Guardian □ Relative _____ □ Parent □ Other _____

Length of relationship:_____ years _____ months

Setting of contact: □ Community □ Home □ Work □ Day Program □ School □ Other _____

Instructions

The Anxiety Depression and Mood Scale (ADAMS) contains a list of behaviors that can be found among individuals with intellectual disability. Please describe the individual's behavior over the last 6 months.

0	behavior has not occurred, or is not a problem
1	behavior occurs occasionally, or is a mild problem
2	behavior occurs quite often, or is a moderate problem
3	behavior occurs a lot, or is a severe problem

	not a problem	mild problem	moderate problem	severe problem
1. Nervous	0	1	2	3
2. Problems initiating communication	0	1	2	3
3. Does not relax or settle down	0	1	2	3
4. Has periods of over-activity	0	1	2	3
5. Sleeps more than normal	0	1	2	3
6. Withdraws from other people	0	1	2	3
7. Tense	0	1	2	3
8. Engages in ritualistic behaviors	0	1	2	3
9. Depressed mood	0	1	2	3
10. Sad	0	1	2	3
11. Worried	0	1	2	3
12. Has developed difficulty staying on task or completing work	0	1	2	3
13. Shy	0	1	2	3
14. Easily fatigued (not due to being overweight)	0	1	2	3
15. Anxious	0	1	2	3
16. Repeatedly checks items	0	1	2	3
17. Easily distracted	0	1	2	3
18. Lacks energy	0	1	2	3
19. Avoids others, spends much of time alone	0	1	2	3
20. Easily upset if ritualistic behaviors are interrupted	0	1	2	3
21. Lacks emotional facial expressions	0	1	2	3
22. Has shown difficulty in starting routine tasks	0	1	2	3
23. Listless	0	1	2	3
24. Experiences panic attacks	0	1	2	3
25. Avoids eye contact	0	1	2	3
26. Trembles when frightening situations are not present.	0	1	2	3
27. Avoids peers	0	1	2	3
28. Tearful	0	1	2	3

Appendix T: The Spence Children's Anxiety Scale – Parent Version

SPENCE CHILDREN'S ANXIETY SCALE (Parent Report)

Your Name: Date: Your Child's Name:

BELOW IS A LIST OF ITEMS THAT DESCRIBE CHILDREN. FOR EACH ITEM PLEASE CIRCLE THE RESPONSE THAT BEST DESCRIBES YOUR CHILD. PLEASE ANSWER ALL THE ITEMS.

1. My child worries about things.....…Never Sometimes Often Always
2. My child is scared of the dark.....Never Sometimes Often Always
3. When my child has a problem, s(he) complains of having a funny feeling in his / her stomach …….....…Never Sometimes Often Always
4. My child complains of feeling afraid.....Never Sometimes Often Always
5. My child would feel afraid of being on his/her own at home…….....Never Sometimes Often Always
6. My child is scared when s(he) has to take a test.....…Never Sometimes Often Always
7. My child is afraid when (s)he has to use public toilets or bathrooms.…….Never Sometimes Often Always
8. My child worries about being away from us / me..... …Never Sometimes Often Always
9. My child feels afraid that (s)he will make a fool of him/herself in front of people.....……....……..Never Sometimes Often Always
10. My child worries that (s)he will do badly at school.....Never Sometimes Often Always
11. My child worries that something awful will happen to someone in our family.....….....……..…….Never Sometimes Often Always
12. My child complains of suddenly feeling as if (s)he can't breathe when there is no reason for this.....……..…Never Sometimes Often Always
13. My child has to keep checking that (s)he has done things right (like the switch is off, or the door is locked)…...Never Sometimes Often Always
14. My child is scared if (s)he has to sleep on his/her own…Never Sometimes Often Always
15. My child has trouble going to school in the mornings because (s)he feels nervous or afraid.....…….Never Sometimes Often Always
16. My child is scared of dogs .....….....Never Sometimes Often Always
17. My child can't seem to get bad or silly thoughts out of his / her head……..Never Sometimes Often Always
18. My child has a problem, s(he) complains of his/her heart beating really fast.....……..Never Sometimes Often Always
19. My child suddenly starts to tremble or shake when there is no reason for this...…….....….....Never Sometimes Often Always
20. My child worries that something bad will happen to him/her…….....Never Sometimes Often Always
21. My child is scared of going to the doctor or dentist ….....Never Sometimes Often Always
22. When my child has a problem, (s)he feels shaky….....Never Sometimes Often Always
23. My child is scared of heights (eg. being at the top of a cliff)…….Never Sometimes Often Always
24. My child has to think special thoughts (like numbers or words) to stop bad things from happening.....….....Never Sometimes Often Always
25. My child feels scared if (s)he has to travel in the car, or on a bus or train …….....…….....……...Never Sometimes Often Always
26. My child worries what other people think of him/her.....Never Sometimes Often Always
27. My child is afraid of being in crowded places (like shopping centres, the movies, buses, busy playgrounds)..Never Sometimes Often Always

28 All of a sudden my child feels really scared for no reason at all.....Never Sometimes Often Always
29. My child is scared of insects or spiders.....…..Never Sometimes Often Always
30. My child complains of suddenly becoming dizzy or faint when there is no reason for this.....……..Never Sometimes Often Always
31. My child feels afraid when (s)he has to talk in front of the class.....…….Never Sometimes Often Always
32. My child's complains of his / her heart suddenly starting to beat too quickly for no reason ……..Never Sometimes Often Always
33. My child worries that (s)he will suddenly get a scared feeling when there is nothing to be afraid of.....…Never Sometimes Often Always
34. My child is afraid of being in small closed places, like tunnels or small rooms.....…..…….....Never Sometimes Often Always
35. My child has to do some things over and over again (like washing his / her hands, cleaning or putting things in a certain order).....……...Never Sometimes Often Always
36. My child gets bothered by bad or silly thoughts or pictures in his/her head ……..…..…….....Never Sometimes Often Always
37. My child has to do certain things in just the right way to stop bad things from happening .....…….....Never Sometimes Often Always
38. My child would feel scared if (s)he had to stay away from home overnight.....…...Never Sometimes Often Always
39. Is there anything else that your child is really afraid of? .....……..…. YES NO
Please write down what it is, and fill out how often (s)he is afraid of this thing:
_____ Never Sometimes Often Always
_____ Never Sometimes Often Always
_____ Never Sometimes Often Always

Appendix U: The Vineland Adaptive Behaviour Scale

About the Individual:

Name: _____

Sex: _____ ID: _____ Grade (if applicable): _____

Highest Grade Completed (if applicable): _____

School or Other Facility (if applicable): _____

Present Classification or Diagnosis: _____

Language Spoken at Home: _____

Age:	**Year**	**Month**	**Day**	Age Used for Starting Points: _____
Interview Date:	_____	_____	_____	Type (circle one): Chronological
Birth Date:	_____	_____	_____	Mental
Chronological Age:	_____	_____	_____	Social

Data from Other Tests: Intelligence _____ Achievement _____ Adaptive Behavior _____ Other _____

Reason for the Interview: _____

Vineland-II™

Record Booklet

Vineland Adaptive Behavior Scales, Second Edition

Survey Interview Form

Sara S. Sparrow, Domenic V. Cicchetti, and David A. Balla

A revision of the *Vineland Social Maturity Scale* by Edgar A. Doll

About the Respondent:

Name: _____

Sex: _____ Telephone: _____

Relationship to Individual: _____

About the Interviewer:

Name: _____

Position: _____

Sex: _____

PEARSON

A 0 9 8 7 6

Product Number 31012

PsychCorp

Communication Domain

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

■ Understanding ♥ Listening and Attending ○ Following Instructions

RECEPTIVE

									✔ Check for Comments below
<1 →	■	1	Turns eyes and head toward sound.	■	2	1	0	DK	
	♥	2	Looks toward parent or caregiver when hearing parent's or caregiver's voice.	♥	2	1	0	DK	
	■	3	Responds to his or her name spoken (for example, turns toward speaker, smiles, etc.).	■	2	1	0	DK	
1 →	■	4	Demonstrates understanding of the meaning of *no*, or word or gesture with the same meaning (for example, stops current activity briefly).	■	2	1	0	DK	
	■	5	Demonstrates understanding of the meaning of *yes*, or word or gesture with the same meaning (for example, continues activity, smiles, etc.).	■	2	1	0	DK	
	♥	6	Listens to story for at least 5 minutes (that is, remains relatively still and directs attention to the storyteller or reader).	♥	2	1	0	DK	
2 →	■	7	Points to at least three major body parts when asked (for example, nose, mouth, hands, feet, etc.).	■	2	1	0	DK	
	■	8	Points to common objects in a book or magazine as they are named (for example, dog, car, cup, key, etc.).	■	2	1	0	DK	
	♥	9	Listens to instructions.	♥	2	1	0	DK	
	○	10	Follows instructions with one action and one object (for example, "Bring me the book"; "Close the door"; etc.).	○	2	1	0	DK	
3+ →	■	11	Points to at least five minor body parts when asked (for example, fingers, elbows, teeth, toes, etc.).	■	2	1	0	DK	
	○	12	Follows instructions with two actions or an action and two objects (for example, "Bring me the crayons and the paper"; "Sit down and eat your lunch"; etc.).	○	2	1	0	DK	
	○	13	Follows instructions in "if-then" form (for example, "If you want to play outside, then put your things away"; etc.).	○	2	1	0	DK	
	♥	14	Listens to a story for at least 15 minutes.	♥	2	1	0	DK	
	♥	15	Listens to a story for at least 30 minutes.	♥	2	1	0	DK	
	○	16	Follows three-part instructions (for example, "Brush your teeth, get dressed, and make your bed"; etc.).	○	2	1	0	DK	
	♥	17	Follows instructions or directions heard 5 minutes before.	♥	2	1	0	DK	
	■	18	Understands sayings that are not meant to be taken word for word (for example, "Button your lip"; "Hit the road"; etc.).	■	2	1	0	DK	
	♥	19	Listens to an informational talk for at least 15 minutes.	♥	2	1	0	DK	
	♥	20	Listens to an informational talk for at least 30 minutes.	♥	2	1	0	DK	

Comments

Item Before Basal ____ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

N/O Total + ☐

Sum of 2s and 1s + ☐

*If the total of DK and/or Missing is greater than 2, do not score subdomain.

Receptive Raw Score = ☐ SUM

Communication Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Pre-Speech Expression · Beginning to Talk · Interactive Speech · Speech Skills · Expressing Complex Ideas

						✔ Check for Comments below
EXPRESSIVE	<1 →		1	Cries or fusses when hungry or wet.	2 1 0 DK	
			2	Smiles when you smile at him or her.	2 1 0 DK	
			3	Makes sounds of pleasure (for example, coos, laughs, etc.).	2 1 0 DK	
			4	Makes nonword baby sounds (that is, babbles).	2 1 0 DK	
			5	Makes sounds or gestures (for example, waves arms) to get parent's or caregiver's attention.	2 1 0 DK	
			6	Makes sounds or gestures (for example, shakes head) if he or she wants an activity to stop or keep going.	2 1 0 DK	
			7	Waves good-bye when another person waves or parent or caregiver tells him or her to wave.	2 1 0 DK	
	1 →		8	Says "Da-da," "Ma-ma," or another name for parent or caregiver (including parent's or caregiver's first name or nickname).	2 1 0 DK	
			9	Points to object he or she wants that is out of reach.	2 1 0 DK	
			10	Points or gestures to indicate preference when offered a choice (for example, "Do you want this one or that one?"; etc.).	2 1 0 DK	
			11	Repeats or tries to repeat common words immediately upon hearing them (for example, *ball, car, go,* etc.).	2 1 0 DK	
			12	Names at least three objects (for example, bottle, dog, favorite toy, etc.).	2 1 0 DK	
			13	Says one-word requests (for example, *up, more, out,* etc.).	2 1 0 DK	
			14	Uses first names or nicknames of brothers, sisters, or friends, or says their names when asked.	2 1 0 DK	
			15	Answers or tries to answer with words when asked a question.	2 1 0 DK	
			16	Names at least 10 objects.	2 1 0 DK	
			17	States own first name or nickname (for example, Latesha, Little Sister, etc.) when asked.	2 1 0 DK	
			18	Uses phrases with a noun and a verb (for example, "Katie stay"; "Go home"; etc.).	2 1 0 DK	
			19	Asks questions by changing inflection of words or simple phrases (for example, "Mine?"; "Me go?"; etc.); grammar is not important.	2 1 0 DK	
	2 →		20	Says at least 50 recognizable words.	2 1 0 DK	
			21	Uses simple words to describe things (for example, *dirty, pretty, big, loud,* etc.).	2 1 0 DK	
			22	Asks questions beginning with *what* or *where* (for example, "What's that?"; "Where doggie go?"; etc.).	2 1 0 DK	

Comments

Communication Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Pre-Speech Expression · Beginning to Talk · Interactive Speech · Speech Skills · Expressing Complex Ideas

EXPRESSIVE, continued

									✔ Check for Comments below
		23	Uses negatives in sentences (for example, "Me no go"; "I won't drink it"; etc.); grammar is not important.		2	1	0	DK	
		24	Tells about experiences in simple sentences (for example, "Ginger and I play"; "Dan read me a book"; etc.).		2	1	0	DK	
		25	Says correct age when asked.		2	1	0	DK	
		26	Says at least 100 recognizable words.		2	1	0	DK	
		27	Uses *in, on,* or *under* in phrases or sentences (for example, "Ball go under chair"; "Put it on the table"; etc.).		2	1	0	DK	
		28	Uses *and* in phrases or sentences (for example, "Mom and Dad"; "I want ice cream and cake"; etc.).		2	1	0	DK	
3 →		29	Says first and last name when asked.		2	1	0	DK	
		30	Identifies and names most common colors (that is, red, blue, green, yellow, orange, purple, brown, and black). Scoring Tip: Mark a "2" if the individual names 6 to 8 colors; mark a "1" if the individual names 2 to 5 colors; mark a "0" if the individual names 0 or 1 color.		2	1	0	DK	
		31	Asks questions beginning with *who* or *why* (for example, "Who's that?"; "Why do I have to go?"; etc.).		2	1	0	DK	
		32	Uses present tense verbs ending in *ing* (for example, "Is singing"; "Is playing"; etc.).		2	1	0	DK	
4, 5 →		33	Uses possessives in phrases or sentences (for example, "That's her book"; "This is Carlos's ball"; etc.).		2	1	0	DK	
		34	Uses pronouns in phrases or sentences; must use correct gender and form of the pronoun, but sentences need not be grammatically correct (for example, "He done it"; "They went"; etc.).		2	1	0	DK	
		35	Asks questions beginning with *when* (for example, "When is dinner?"; "When can we go home?"; etc.).		2	1	0	DK	
		36	Uses regular past tense verbs (for example, *walked, baked,* etc.); may use irregular past tense verbs ungrammatically (for example, "I runned away"; etc.).		2	1	0	DK	
		37	Uses *behind* or *in front of* in phrases or sentences (for example, "I walked in front of her"; "Terrell is behind you"; etc.).		2	1	0	DK	
		38	Pronounces words clearly without sound substitutions (for example, does not say "wabbit" for "rabbit," "Thally" for "Sally," etc.).		2	1	0	DK	
		39	Tells basic parts of a story, fairy tale, or television show plot; does not need to include great detail or recount in perfect order.		2	1	0	DK	
6 →		40	Says month and day of birthday when asked.		2	1	0	DK	
		41	Modulates tone of voice, volume, and rhythm appropriately (for example, does not consistently speak too loudly, too softly, or in a monotone, etc.).		2	1	0	DK	

Comments

Communication Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Pre-Speech Expression · Beginning to Talk · Interactive Speech · Speech Skills · Expressing Complex Ideas

EXPRESSIVE, continued

								✔ Check for Comments below
	☆	42	Tells about experiences in detail (for example, tells who was involved, where activity took place, etc.).	☆	2	1	0	DK	
	☆	43	Gives simple directions (for example, on how to play a game or how to make something). Scoring Tip: Mark a "2" if the directions are clear enough to follow; mark a "1" if the individual articulates directions but they are not clear enough to follow; mark a "0" if the individual never attempts to articulate directions.	☆	2	1	0	DK	
	◠	44	Uses *between* in phrases or sentences (for example, "The ball went between the cars"; etc.).	◠	2	1	0	DK	
7+ →	💬	45	Says own telephone number when asked.	💬	2	1	0	DK	
	💬	46	Easily moves from one topic to another in conversation.	💬	2	1	0	DK	
	💬	47	Stays on topic in conversations; does not go off on tangents.	💬	2	1	0	DK	
	☆	48	Explains ideas in more than one way (for example, "This was a good book. It was exciting and fun to read"; etc.).	☆	2	1	0	DK	
	◠	49	Has conversations that last 10 minutes (for example, relates experiences, contributes ideas, shares feelings, etc.).	◠	2	1	0	DK	
	◠	50	Uses irregular plurals correctly (for example, *children, geese, mice, women,* etc.).	◠	2	1	0	DK	
	💬	51	Says complete home address (that is, street or rural route, apartment number, city, and state), with or without zip code, when asked.	💬	2	1	0	DK	
	☆	52	Describes a short-term goal and what he or she needs to do to reach it (for example, says, "I want to get an A on my test, so I'm going to study hard"; etc.).	☆	2	1	0	DK	
	☆	53	Gives complex directions to others (for example, to a distant location, for recipe with many ingredients or steps, etc.). Scoring Tip: Mark a "2" if the directions are clear enough to follow; mark a "1" if the individual articulates directions but they are not clear enough to follow; mark a "0" if the individual never attempts to articulate directions.	☆	2	1	0	DK	
	☆	54	Describes a realistic long-range goal that can be done in 6 months or more (for example, says, "I want to buy a bike, so I'll babysit and run errands to earn enough money to buy it"; etc.).	☆	2	1	0	DK	

Comments

Item Before Basal ____ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

N/O Total + ☐

Sum of 2s and 1s + ☐

*If the total of DK and/or Missing is greater than 2, do not score subdomain.

Expressive Raw Score = ☐ SUM

Communication Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Beginning to Read | Reading Skills | Writing Skills

WRITTEN

						✔ Check for Comments below
3–5 →		1	Identifies one or more alphabet letters as letters and distinguishes them from numbers.		2 1 0 DK	
		2	Recognizes own name in printed form.		2 1 0 DK	
		3	Identifies at least 10 printed letters of the alphabet.		2 1 0 DK	
		4	Prints or writes using correct orientation (for example, in English from left to right; in some languages from right to left or top to bottom).		2 1 0 DK	
		5	Copies own first name.		2 1 0 DK	
		6	Identifies all printed letters of the alphabet, upper- and lowercase.		2 1 0 DK	
		7	Prints at least three simple words from example (for example, *cat, see, bee,* etc.).		2 1 0 DK	
6 →		8	Prints or writes own first and last name from memory.		2 1 0 DK	
		9	Reads at least 10 words aloud.		2 1 0 DK	
		10	Prints at least 10 simple words from memory (for example, *hat, ball, the,* etc.).		2 1 0 DK	
		11	Reads simple stories aloud (that is, stories with sentences of three to five words).		2 1 0 DK	
7, 8 →		12	Prints simple sentences of three or four words; may make small errors in spelling or sentence structure.		2 1 0 DK	
		13	Prints more than 20 words from memory; may make small spelling errors.		2 1 0 DK	
		14	Reads and understands material of at least second-grade level.		2 1 0 DK	
		15	Puts lists of words in alphabetical order.		2 1 0 DK	
9+ →		16	Writes simple correspondence at least three sentences long (for example, postcards, thank-you notes, e-mail, etc.).		2 1 0 DK	
		17	Reads and understands material of at least fourth-grade level.		2 1 0 DK	
		18	Writes reports, papers, or essays at least one page long; may use computer.		2 1 0 DK	
		19	Writes complete mailing and return addresses on letters or packages.		2 1 0 DK	
		20	Reads and understands material of at least sixth-grade level.		2 1 0 DK	
		21	Edits or corrects own written work before handing it in (for example, checks punctuation, spelling, grammar, etc.).		2 1 0 DK	
		22	Writes advanced correspondence at least 10 sentences long; may use computer.		2 1 0 DK	
		23	Reads and understands material of at least ninth-grade level.		2 1 0 DK	
		24	Reads at least two newspaper articles weekly (print or electronic version).		2 1 0 DK	
		25	Writes business letters (for example, requests information, makes complaint, places order, etc.); may use computer.		2 1 0 DK	

Comments

Item Before Basal ☐ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

N/O Total + ☐

Sum of 2s and 1s + ☐

**If the total of DK and/or Missing is greater than 2, do not score subdomain.*

Written Raw Score = ☐ SUM

Daily Living Skills Domain

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Eating and Drinking · Toileting · Dressing · Bathing · Grooming · Health Care

PERSONAL

						✔ Check for Comments below
<1 →		1	Opens mouth when food is offered.		2 1 0 DK	
		2	Eats solid foods (for example, cooked vegetables, chopped meats, etc.).		2 1 0 DK	
		3	Sucks or chews on finger foods (for example, crackers, cookies, toast, etc.).		2 1 0 DK	
1 →		4	Drinks from a cup or glass; may spill.		2 1 0 DK	
		5	Lets someone know when he or she has wet or soiled diaper or pants (for example, points, vocalizes, pulls at diaper, etc.).		2 1 0 DK	
		6	Feeds self with spoon; may spill.		2 1 0 DK	
		7	Sucks from straw.		2 1 0 DK	
		8	Takes off clothing that opens in the front (for example, a coat or sweater); does not have to unbutton or unzip the clothing.		2 1 0 DK	
2 →		9	Pulls up clothing with elastic waistbands (for example, underwear or sweatpants).		2 1 0 DK	
		10	Feeds self with fork; may spill.		2 1 0 DK	
		11	Drinks from a cup or glass without spilling.		2 1 0 DK	
		12	Feeds self with spoon without spilling.		2 1 0 DK	
3 →		13	Urinates in toilet or potty chair.		2 1 0 DK	
		14	Puts on clothing that opens in the front (for example, a coat or sweater); does not have to zip or button the clothing.		2 1 0 DK	
		15	Asks to use toilet.		2 1 0 DK	
		16	Defecates in toilet or potty chair.		2 1 0 DK	
		17	Is toilet-trained during the day. Scoring Tip: Mark "2" if the individual uses the toilet without help and without accidents; mark "1" if the individual needs help, such as with wiping, or has some accidents; mark "0" if the individual always needs help or has frequent accidents.		2 1 0 DK	
4 →		18	Zips zippers that are fastened at the bottom (for example, in pants, on backpacks, etc.).		2 1 0 DK	
		19	Wipes or blows nose using tissue or handkerchief.		2 1 0 DK	
		20	Is toilet-trained during the night.		2 1 0 DK	
		21	Puts shoes on correct feet; does not need to tie laces.		2 1 0 DK	
		22	Fastens snaps.		2 1 0 DK	
		23	Holds spoon, fork, and knife correctly.		2 1 0 DK	

Comments

Daily Living Skills Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Eating and Drinking · Toileting · Dressing · Bathing · Grooming · Health Care

✔ Check for Comment below

PERSONAL, continued

	24	Washes and dries face using soap and water.		2	1	0	DK	
5, 6 →	25	Brushes teeth.		2	1	0	DK	
		Scoring Tip: Mark a "2" if the individual brushes teeth without help, including putting toothpaste on the brush, and without being told to brush; mark "1" if the individual needs help brushing or putting toothpaste on the brush or needs frequent reminders; mark "0" if the individual never brushes without help or without being reminded.						
	26	Buttons large buttons in front, in correct buttonholes.		2	1	0	DK	
	27	Covers mouth and nose when coughing and sneezing.		2	1	0	DK	
	28	Buttons small buttons in front, in correct buttonholes.		2	1	0	DK	
	29	Connects and zips zippers that are not fastened at the bottom (for example, in jackets, sweatshirts, etc.).		2	1	0	DK	
	30	Turns faucets on and adjusts temperature by adding hot or cold water.		2	1	0	DK	
	31	Wears appropriate clothing during wet or cold weather (for example, raincoat, boots, sweater, etc.).		2	1	0	DK	
7+ →	32	Bathes or showers and dries self.		2	1	0	DK	
		Scoring Tip: Mark a "2" if the individual bathes or showers without help, including turning the water on and off; mark a "1" if the individual needs help with any part of bathing or drying or with turning the water on and off; mark "0" if the individual never bathes or showers without help or without reminders.						
	33	Finds and uses appropriate public restroom for his or her gender.		2	1	0	DK	
	34	Washes and dries hair (with towel or hair dryer).		2	1	0	DK	
	35	Cares for minor cuts (for example, cleans wound, puts on a bandage, etc.).		2	1	0	DK	
	36	Takes medicine as directed (that is, follows directions on label).		2	1	0	DK	
	37	Uses thermometer to take own or another's temperature.		2	1	0	DK	
	38	Seeks medical help in an emergency (for example, recognizes symptoms of serious illness or injury, such as shortness of breath, chest pain, uncontrolled bleeding, etc.).		2	1	0	DK	
		Scoring Tip: You may mark "N/O" for No Opportunity if the individual has not been in a medical emergency.			N/O			
	39	Follows directions for health care procedures, special diet, or medical treatments.		2	1	0	DK	
		Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a health concern that requires special procedures, diet, or treatments.			N/O			
	40	Keeps track of medications (nonprescription and prescription) and refills them as needed.		2	1	0	DK	
	41	Makes appointments for regular medical and dental checkups.		2	1	0	DK	

Comments

Item Before Basal ____ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

N/O Total + ☐

Sum of 2s and 1s + ☐

Personal Raw Score = ☐ SUM

**If the total of DK and/or Missing is greater than 2, do not score subdomain.*

Daily Living Skills Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Safety at Home · Kitchen Chores · Housekeeping

DOMESTIC

				✔ Check for Comments below
1–6 →	1	Is careful around hot objects (for example, the stove or oven, an open fire, etc.).	2 1 0 DK	
	2	Helps with simple household chores (for example, dusts, picks up clothes or toys, feeds pet, etc.).	2 1 0 DK	
	3	Clears unbreakable items from own place at table.	2 1 0 DK	
	4	Cleans up play or work area at end of an activity (for example, finger painting, model building, etc.).	2 1 0 DK	
	5	Puts away personal possessions (for example, toys, books, magazines, etc.).	2 1 0 DK	
7–10 →	6	Is careful when using sharp objects (for example, scissors, knives, etc.).	2 1 0 DK	
	7	Clears breakable items from own place at table.	2 1 0 DK	
	8	Helps prepare foods that require mixing and cooking (for example, cake or cookie mixes, macaroni and cheese, etc.).	2 1 0 DK	
	9	Uses simple appliances (for example, a toaster, can opener, bottle opener, etc.).	2 1 0 DK	
	10	Uses microwave oven for heating, baking, or cooking (that is, sets time and power setting, etc.). Scoring Tip: You may mark "N/O" for No Opportunity if there is no microwave in the home.	2 1 0 DK N/O	
	11	Puts clean clothes away in proper place (for example, in drawers or closet, on hooks, etc.).	2 1 0 DK	
11+ →	12	Uses tools (for example, a hammer to drive nails, a screwdriver to screw and unscrew screws, etc.).	2 1 0 DK	
	13	Washes dishes by hand, or loads and uses dishwasher.	2 1 0 DK	
	14	Sweeps, mops, or vacuums floors thoroughly. Scoring Tip: Mark "2" if the individual mops, sweeps, or vacuums so well that the task does not have to be redone; mark a "1" if the individual doesn't consistently complete the task well; mark a "0" if the individual never mops, sweeps, or vacuums, or does the task so poorly that it always needs to be redone.	2 1 0 DK	
	15	Clears table completely (for example, scrapes and stacks dishes, throws away disposable items, etc.).	2 1 0 DK	
	16	Uses household products correctly (for example, laundry detergent, furniture polish, glass cleaner, etc.).	2 1 0 DK	
	17	Prepares basic foods that do not need mixing but require cooking (for example, rice, soup, vegetables, etc.).	2 1 0 DK	
	18	Cleans one or more rooms other than own bedroom.	2 1 0 DK	
	19	Uses sharp knife to prepare food.	2 1 0 DK	
	20	Uses stove or oven for heating, baking, or cooking (that is, turns burners on and off, sets oven temperature, etc.).	2 1 0 DK	
	21	Prepares food from ingredients that require measuring, mixing, and cooking.	2 1 0 DK	
	22	Washes clothing as needed.	2 1 0 DK	
	23	Performs maintenance tasks as needed (for example, replaces light bulbs, changes vacuum cleaner bag, etc.).	2 1 0 DK	
	24	Plans and prepares main meal of the day.	2 1 0 DK	

Comments

Item Before Basal ____ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

N/O Total + ☐

Sum of 2s and 1s + ☐

*If the total of DK and/or Missing is greater than 2, do not score subdomain.

Domestic Raw Score = ☐ SUM

Daily Living Skills Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Telephone Skills · Rules, Rights, and Safety · Time and Dates · Job Skills · Computer Skills · Money Skills · Restaurant Skills · Television and Radio · Going Places Independently

✔ Check for Comments below

COMMUNITY

1–3 →	☎	1	Demonstrates understanding of function of telephone (for example, pretends to talk on phone, etc.).	2 1 0 DK
	☎	2	Talks to familiar person on telephone.	2 1 0 DK
	☐	3	Uses TV or radio without help (for example, turns equipment on, accesses channel or station, selects program, etc.).	2 1 0 DK
			Scoring Tip: You may mark "N/O" for No Opportunity if there is no TV or radio in the home.	N/O
4 →	$	4	Counts at least 10 objects, one by one.	2 1 0 DK
	●	5	Is aware of and demonstrates appropriate behavior while riding in car (for example, keeps seat belt on, refrains from distracting driver, etc.).	2 1 0 DK
	$	6	Demonstrates understanding of the function of money (for example, says, "Money is what you need to buy things at the store"; etc.).	2 1 0 DK
	●	7	Uses sidewalk (where available) or shoulder of road when walking or using wheeled equipment (for example, skates, scooter, tricycle, etc.).	2 1 0 DK
5, 6 →	🕐	8	Demonstrates understanding of function of clock (for example, says, "Clocks tell time"; "What time can we go?"; etc.).	2 1 0 DK
	●	9	Follows household rules (for example, no running in the house, no jumping on the furniture, etc.).	2 1 0 DK
	💾	10	Demonstrates computer skills necessary to play games or start programs with computer turned on; does not need to turn computer on by self.	2 1 0 DK
			Scoring Tip: You may mark "N/O" for No Opportunity if there is no computer in the home.	N/O
	☎	11	Summons to the telephone the person receiving a call or indicates that the person is not available.	2 1 0 DK
	$	12	Identifies penny, nickel, dime, and quarter by name when asked; does not need to know the value of coins.	2 1 0 DK
	●	13	Looks both ways when crossing streets or roads.	2 1 0 DK
7 →	🕐	14	Says current day of the week when asked.	2 1 0 DK
	●	15	Demonstrates understanding of right to personal privacy for self and others (for example, while using restroom or changing clothes, etc.).	2 1 0 DK
	●	16	Demonstrates knowledge of what phone number to call in an emergency when asked.	2 1 0 DK
	🕐	17	Tells time using a digital clock or watch.	2 1 0 DK
8 →	$	18	States value of penny (1 cent), nickel (5 cents), dime (10 cents), and quarter (25 cents).	2 1 0 DK
	$	19	Discriminates between bills of different denominations (for example, refers to $1 bills, $5 bills, etc., in conversation; etc.).	2 1 0 DK
	●	20	Obeys traffic lights and *Walk* and *Don't Walk* signs.	2 1 0 DK
	🕐	21	Points to current or other date on calendar when asked.	2 1 0 DK
	$	22	Demonstrates understanding that some items cost more than others (for example, says, "I have enough money to buy gum but not a candy bar"; "Which pencil costs less?"; etc.).	2 1 0 DK
9–11 →	🕐	23	Tells time by the half hour on analog clock (for example, 1:30, 2:00, etc.).	2 1 0 DK
	☎	24	Makes telephone calls to others, using standard or cell phone.	2 1 0 DK

Comments

Daily Living Skills Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Telephone Skills · Rules, Rights, and Safety · Time and Dates · Job Skills · Computer Skills · Money Skills · Restaurant Skills · Television and Radio · Going Places Independently

✔ Check for Comments below

COMMUNITY, continued

	25	Orders a complete meal in a fast-food restaurant. Scoring Tip: You may mark "N/O" for No Opportunity if individual has not eaten at a fast-food restaurant.		2 1 0 / N/O	DK	
12–15→	26	Carries or stores money safely (for example, in wallet, purse, money belt, etc.).		2 1 0	DK	
	27	Tells time by 5-minute segments on analog clock (for example, 1:05, 1:10, etc.).		2 1 0	DK	
	28	Obeys curfew parent or caregiver sets.		2 1 0	DK	
	29	Watches or listens to programs for information (for example, weather report, news, educational program, etc.). Scoring Tip: You may mark "N/O" for No Opportunity if there is no TV or radio in the home.		2 1 0 / N/O	DK	
	30	Counts change from a purchase.		2 1 0	DK	
	31	Demonstrates computer skills necessary to carry out complex tasks (for example, word processing, accessing the Internet, installing software, etc.). Scoring Tip: You may mark "N/O" for No Opportunity if there is no computer in the home.		2 1 0 / N/O	DK	
16+ →	32	Evaluates quality and price when selecting items to purchase.		2 1 0	DK	
	33	Obeys time limits for breaks (for example, lunch or coffee breaks, etc.).		2 1 0	DK	
	34	Travels at least 5 to 10 miles to familiar destination (that is, bikes, uses public transportation, or drives self).		2 1 0	DK	
	35	Demonstrates understanding of right to complain or report legitimate problems when dissatisfied with services or situations.		2 1 0	DK	
	36	Notifies school or supervisor when he or she will be late or absent.		2 1 0	DK	
	37	Uses savings or checking account responsibly (for example, keeps some money in account, tracks balance carefully, etc.).		2 1 0	DK	
	38	Travels at least 5 to 10 miles to unfamiliar destination (that is, bikes, uses public transportation, or drives self).		2 1 0	DK	
	39	Earns money at part-time job (that is, at least 10 hours a week) for 1 year. Scoring Tip: Do not mark 1.		2 ~~1~~ 0	DK	
	40	Attempts to improve job performance after receiving constructive criticism from supervisor. Scoring Tip: You may mark "N/O" for No Opportunity if the individual has not held a job.		2 1 0 / N/O	DK	
	41	Manages own money (for example, pays most or all own expenses, uses checks or money orders for purchases as needed, etc.).		2 1 0	DK	
	42	Has held full-time job for 1 year. Scoring Tip: Do not mark 1.		2 ~~1~~ 0	DK	
	43	Budgets for monthly expenses (for example, utilities, rent, etc.).		2 1 0	DK	
	44	Applies for and uses personal credit card responsibly (for example, does not exceed credit limit, pays on time, etc.).		2 1 0	DK	

Comments

Item Before Basal ____ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

N/O Total + ☐

Sum of 2s and 1s + ☐

**If the total of DK and/or Missing is greater than 2, do not score subdomain.*

Community Raw Score = ☐ SUM

Socialization Domain

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Responding to Others · Expressing and Recognizing Emotions · Imitating · Social Communication · Thoughtfulness · Friendship · Dating

								✔ Check for Comments below
INTERPERSONAL RELATIONSHIPS	<1 →		1	Looks at face of parent or caregiver.		2	1	0	DK	
			2	Watches (that is, follows with eyes) someone moving by crib or bed for 5 seconds or more.		2	1	0	DK	
			3	Shows two or more emotions (for example, laughs, cries, screams, etc.).		2	1	0	DK	
			4	Smiles or makes sounds when approached by a familiar person.		2	1	0	DK	
			5	Makes or tries to make social contact (for example, smiles, makes noises, etc.).		2	1	0	DK	
			6	Reaches for familiar person when person holds out arms to him or her.		2	1	0	DK	
			7	Shows preference for certain people and objects (for example, smiles, reaches for or moves toward person or object, etc.).		2	1	0	DK	
			8	Shows affection to familiar persons (for example, touches, hugs, kisses, cuddles, etc.).		2	1	0	DK	
			9	Imitates or tries to imitate parent's or caregiver's facial expressions (for example, smiles, frowns, etc.).		2	1	0	DK	
			10	Moves about looking for parent or caregiver or other familiar person nearby.		2	1	0	DK	
	1, 2 →		11	Shows interest in children the same age, other than brothers or sisters (for example, watches them, smiles at them, etc.).		2	1	0	DK	
			12	Imitates simple movements (for example, claps hands, waves good-bye, etc.).		2	1	0	DK	
			13	Uses actions to show happiness or concern for others (for example, hugs, pats arm, holds hands, etc.).		2	1	0	DK	
			14	Shows desire to please others (for example, shares a snack or toy, tries to help even if not capable, etc.).		2	1	0	DK	
	3, 4 →		15	Demonstrates friendship-seeking behavior with others the same age (for example, says, "Do you want to play?" or takes another child by the hand, etc.).		2	1	0	DK	
			16	Imitates relatively complex actions as they are being performed by another person (for example, shaving, putting on makeup, hammering nails, etc.).		2	1	0	DK	
			17	Answers when familiar adults make small talk (for example, if asked, "How are you?" says, "I'm fine"; if told, "You look nice," says, "Thank you"; etc.).		2	1	0	DK	
			18	Repeats phrases heard spoken before by an adult (for example, "Honey, I'm home"; "No dessert until you clean your plate"; etc.).		2	1	0	DK	
			19	Uses words to express own emotions (for example, "I'm happy"; "I'm scared"; etc.).		2	1	0	DK	
	5 →		20	Has best friend or shows preference for certain friends (of either sex) over others.		2	1	0	DK	
			21	Imitates relatively complex actions several hours after watching someone else perform them (for example, shaving, putting on makeup, hammering nails, etc.).		2	1	0	DK	

Comments

Socialization Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Responding to Others | Expressing and Recognizing Emotions | Imitating | Social Communication | Thoughtfulness | Friendship | Dating

✔ Check for Comments below

INTERPERSONAL RELATIONSHIPS, continued

	22	Uses words to express happiness or concern for others (for example, says, "Yeah! You won"; "Are you all right?"; etc.).	2 1 0	DK	
	23	Acts when another person needs a helping hand (for example, holds door open, picks up dropped items, etc.).	2 1 0	DK	
6–8 →	24	Recognizes the likes and dislikes of others (for example, says, "Chow likes soccer"; "Susie doesn't eat pizza"; etc.).	2 1 0	DK	
	25	Shows same level of emotion as others around him or her (for example, does not downplay or overdramatize a situation, etc.).	2 1 0	DK	
	26	Keeps comfortable distance between self and others in social situations (for example, does not get too close to another person when talking, etc.).	2 1 0	DK	
	27	Talks with others about shared interests (for example, sports, TV shows, summer plans, etc.).	2 1 0	DK	
9+ →	28	Starts small talk when meets people he or she knows (for example, says, "How are you?"; "What's up?"; etc.).	2 1 0	DK	
	29	Meets with friends regularly.	2 1 0	DK	
	30	Chooses not to say embarrassing or mean things or ask rude questions in public.	2 1 0	DK	
	31	Places reasonable demands on friendship (for example, does not expect to be a person's only friend or to have the friend always available, etc.).	2 1 0	DK	
	32	Understands that others do not know his or her thoughts unless he or she says them.	2 1 0	DK	
	33	Is careful when talking about personal things.	2 1 0	DK	
	34	Cooperates with others to plan or be part of an activity (for example, a birthday party, sports event, etc.).	2 1 0	DK	
	35	Demonstrates understanding of hints or indirect cues in conversation (for example, knows that yawns may mean, "I'm bored," or a quick change of subject may mean, "I don't want to talk about that"; etc.).	2 1 0	DK	
	36	Starts conversations by talking about things that interest others (for example, says, "Tyrone tells me you like computers"; etc.).	2 1 0	DK	
	37	Goes on group dates.	2 1 0	DK	
	38	Goes on single dates.	2 1 0	DK	

Comments

Item Before Basal ____ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

Sum of 2s and 1s + ☐

Interpersonal Relationships Raw Score = ☐ SUM

**If the total of DK and/or Missing is greater than 2, do not score subdomain.*

Socialization Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Playing · Sharing and Cooperating · Going Places with Friends · Playing Games · Recognizing Social Cues

					✔ Check for Comments below
PLAY AND LEISURE TIME					
<1 →		1	Responds when parent or caregiver is playful (for example, smiles, laughs, claps hands, etc.).	2 1 0 DK	
		2	Shows interest in where he or she is (for example, looks or moves around, touches objects or people, etc.).	2 1 0 DK	
		3	Plays simple interaction games with others (for example, peekaboo, patty-cake, etc.).	2 1 0 DK	
1, 2 →		4	Plays near another child, each doing different things.	2 1 0 DK	
		5	Chooses to play with other children (for example, does not stay on the edge of a group or avoid others).	2 1 0 DK	
		6	Plays cooperatively with one or more children for up to 5 minutes.	2 1 0 DK	
		7	Plays cooperatively with more than one child for more than 5 minutes.	2 1 0 DK	
		8	Continues playing with another child with little fussing when parent or caregiver leaves.	2 1 0 DK	
3 →		9	Shares toys or possessions when asked.	2 1 0 DK	
		10	Plays with others with minimal supervision.	2 1 0 DK	
		11	Uses common household objects or other objects for make-believe activities (for example, pretends a block is a car, a box is a house, etc.).	2 1 0 DK	
		12	Protects self by moving away from those who destroy things or cause injury (for example, those who bite, hit, throw things, pull hair, etc.).	2 1 0 DK	
4 →		13	Plays simple make-believe activities with others (for example, plays dress-up, pretends to be superheroes, etc.).	2 1 0 DK	
		14	Seeks out others for play or companionship (for example, invites others home, goes to another's home, plays with others on the playground, etc.).	2 1 0 DK	
		15	Takes turns when asked while playing games or sports.	2 1 0 DK	
		16	Plays informal, outdoor group games (for example, tag, jump rope, catch, etc.).	2 1 0 DK	
		17	Shares toys or possessions without being asked.	2 1 0 DK	
5, 6 →		18	Follows rules in simple games (relay races, spelling bees, electronic games, etc.).	2 1 0 DK	
		19	Takes turns without being asked.	2 1 0 DK	
		20	Plays simple card or board game based only on chance (for example, Go Fish, Crazy Eights, Sorry™, etc.).	2 1 0 DK	
7–12 →		21	Goes places with friends during the day with adult supervision (for example, to a shopping mall, park, community center, etc.).	2 1 0 DK	
		22	Asks permission before using objects belonging to or being used by another.	2 1 0 DK	

Comments

Socialization Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Playing · Sharing and Cooperating · Going Places with Friends · Playing Games · Recognizing Social Cues

✔ Check for Comments below

PLAY AND LEISURE TIME, continued

	23	Refrains from entering group when nonverbal cues indicate that he or she is not welcome.	2 1 0	DK
	24	Plays simple games that require keeping score (for example, kickball, pickup basketball, etc.).	2 1 0	DK
13+ →	25	Shows good sportsmanship (that is, follows rules, is not overly aggressive, congratulates other team on winning, and does not get mad when losing).	2 1 0	DK
	26	Plays more than one board, card, or electronic game requiring skill and decision making (for example, Monopoly™, Cribbage, etc.).	2 1 0	DK
	27	Goes places with friends in evening with adult supervision (for example, to a concert, lecture, sporting event, movie, etc.).	2 1 0	DK
	28	Follows rules in complex games or sports (for example, football, soccer, volleyball, etc.).	2 1 0	DK
	29	Goes places with friends during the day without adult supervision (for example, to a shopping mall, park, community center, etc.).	2 1 0	DK
	30	Plans fun activities with more than two things to be arranged (for example, a trip to a beach or park that requires planning transportation, food, recreational items, etc.).	2 1 0	DK
	31	Goes places with friends in evening without adult supervision (for example, to a concert, lecture, sporting event, movie, etc.).	2 1 0	DK

Comments

Item Before Basal ☐ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

Sum of 2s and 1s + ☐

Play and Leisure Time Raw Score = ☐ SUM

**If the total of DK and/or Missing is greater than 2, do not score subdomain.*

Manners · Apologizing · Responsibility · Appropriate Social Caution · Transitions · Controlling Impulses · Keeping Secrets

COPING SKILLS

1–4 →	1	Changes easily from one at-home activity to another.	2 1 0	DK
	2	Says "thank you" when given something.	2 1 0	DK
	3	Changes behavior depending on how well he or she knows another person (for example, acts differently with family member than with stranger, etc.).	2 1 0	DK
	4	Chews with mouth closed.	2 1 0	DK
5–7 →	5	Says "please" when asking for something.	2 1 0	DK
	6	Ends conversations appropriately (for example, says, "Good-bye"; "See you later"; etc.).	2 1 0	DK
	7	Cleans or wipes face and hands during and/or after meals.	2 1 0	DK
	8	Responds appropriately to reasonable changes in routine (for example, refrains from complaining, etc.).	2 1 0	DK

Socialization Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Manners · Apologizing · Responsibility · Appropriate Social Caution
Transitions · Controlling Impulses · Keeping Secrets

COPING SKILLS, continued

				✔ Check for Comments below
8 →	Apologizing	9	Says that he or she is sorry for unintended mistakes (for example, bumping into someone, etc.).	2 1 0 DK
	Controlling Impulses	10	Chooses not to taunt, tease, or bully.	2 1 0 DK
	Manners	11	Acts appropriately when introduced to strangers (for example, nods, smiles, shakes hands, greets them, etc.).	2 1 0 DK
	Manners	12	Changes voice level depending on location or situation (for example, in a library, during a movie or play, etc.).	2 1 0 DK
	Apologizing	13	Says he or she is sorry after hurting another's feelings.	2 1 0 DK
	Manners	14	Refrains from talking with food in mouth.	2 1 0 DK
	Manners	15	Talks with others without interrupting or being rude.	2 1 0 DK
9–12 →	Controlling Impulses	16	Accepts helpful suggestions or solutions from others.	2 1 0 DK
	Controlling Impulses	17	Controls anger or hurt feelings when plans change for reason(s) that cannot be helped (for example, bad weather, car trouble, etc.).	2 1 0 DK
	Keeping Secrets	18	Keeps secrets or confidences for longer than one day.	2 1 0 DK
	Apologizing	19	Says he or she is sorry after making unintentional mistakes or errors in judgment (for example, when unintentionally leaving someone out of a game, etc.).	2 1 0 DK
	Controlling Impulses	20	Shows understanding that gentle teasing with family and friends can be a form of humor or affection.	2 1 0 DK
13+ →	Responsibility	21	Tells parent or caregiver about his or her plans (for example, what time he or she is leaving and returning, where he or she is going, etc.).	2 1 0 DK
	Appropriate Social Caution	22	Chooses to avoid dangerous or risky activities (for example, jumping off high places, picking up a hitchhiker, driving recklessly, etc.).	2 1 0 DK
	Controlling Impulses	23	Controls anger or hurt feelings when he or she does not get his or her way (for example, when not allowed to watch television or attend a party; when suggestion is rejected by friend or supervisor; etc.).	2 1 0 DK
	Responsibility	24	Follows through with arrangements (for example, if promises to meet someone, meets that person; etc.).	2 1 0 DK
	Appropriate Social Caution	25	Stops or stays away from relationships or situations that are hurtful or dangerous (for example, being bullied or made fun of, being taken advantage of sexually or financially, etc.).	2 1 0 DK
	Controlling Impulses	26	Controls anger or hurt feelings due to constructive criticism (for example, correction of misbehavior, discussion of test score or grade, performance review, etc.).	2 1 0 DK
	Keeping Secrets	27	Keeps secrets or confidences for as long as needed.	2 1 0 DK
	Controlling Impulses	28	Thinks about what could happen before making decisions (for example, refrains from acting impulsively, thinks about important information, etc.).	2 1 0 DK
	Appropriate Social Caution	29	Is aware of potential danger and uses caution when encountering risky social situations (for example, binge drinking parties, Internet chat rooms, personal ads, etc.).	2 1 0 DK
	Responsibility	30	Shows respect for co-workers (for example, does not distract or interrupt others who are working, is on time for meetings, etc.).	2 1 0 DK

Comments

Item Before Basal ☐ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

Sum of 2s and 1s + ☐

Coping Skills Raw Score = ☐ SUM

**If the total of DK and/or Missing is greater than 2, do not score subdomain.*

Motor Skills Domain

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Sitting | Walking and Running | Play Activity | Standing | Creeping and Crawling

✔ Check for Comments below

GROSS

<1 →	Sitting	1	Holds head erect for at least 15 seconds when held upright in parent's or caregiver's arms.	Sitting	2 1 0 DK
	Sitting	2	Sits supported (for example, in a chair, with pillows, etc.) for at least 1 minute.	Sitting	2 1 0 DK
	Sitting	3	Sits without support for at least 1 minute.	Sitting	2 1 0 DK
	Creeping and Crawling	4	Creeps or moves on stomach across floor.	Creeping and Crawling	2 1 0 DK
	Sitting	5	Sits without support for at least 10 minutes.	Sitting	2 1 0 DK
	Sitting	6	Raises self to sitting position and sits without support for at least 1 minute.	Sitting	2 1 0 DK
	Creeping and Crawling	7	Crawls at least 5 feet on hands and knees, without stomach touching floor	Creeping and Crawling	2 1 0 DK
1 →	Standing	8	Pulls self to standing position.	Standing	2 1 0 DK
	Creeping and Crawling	9	Crawls up stairs.	Creeping and Crawling	2 1 0 DK
	Walking and Running	10	Takes at least two steps.	Walking and Running	2 1 0 DK
	Standing	11	Stands alone for 1 to 3 minutes.	Standing	2 1 0 DK
	Play Activity	12	Rolls ball while sitting.	Play Activity	2 1 0 DK
	Play Activity	13	Climbs on and off low objects (for example, chair, step stool, slide, etc.).	Play Activity	2 1 0 DK
	Creeping and Crawling	14	Crawls down stairs.	Creeping and Crawling	2 1 0 DK
	Standing	15	Stands for at least 5 minutes.	Standing	2 1 0 DK
	Walking and Running	16	Walks across room; may be unsteady and fall occasionally.	Walking and Running	2 1 0 DK
2 →	Play Activity	17	Throws ball.	Play Activity	2 1 0 DK
	Walking and Running	18	Walks to get around; does not need to hold on to anything.	Walking and Running	2 1 0 DK
	Play Activity	19	Climbs on and off adult-sized chair.	Play Activity	2 1 0 DK
	Walking and Running	20	Runs without falling; may be awkward and uncoordinated.	Walking and Running	2 1 0 DK
	Walking and Running	21	Walks up stairs, putting both feet on each step; may use railing.	Walking and Running	2 1 0 DK
	Play Activity	22	Kicks ball.	Play Activity	2 1 0 DK
3 →	Walking and Running	23	Runs smoothly without falling.	Walking and Running	2 1 0 DK
	Walking and Running	24	Walks down stairs, facing forward, putting both feet on each step; may use railing.	Walking and Running	2 1 0 DK
	Play Activity	25	Jumps with both feet off floor.	Play Activity	2 1 0 DK
	Play Activity	26	Throws ball of any size in specific direction.	Play Activity	2 1 0 DK
	Play Activity	27	Catches beach ball-sized ball with both hands from a distance of 2 or 3 feet.	Play Activity	2 1 0 DK
	Walking and Running	28	Walks up stairs, alternating feet; may use railing.	Walking and Running	2 1 0 DK
	Play Activity	29	Pedals tricycle or other three-wheeled toy for at least 6 feet.	Play Activity	2 1 0 DK
			Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a tricycle or three-wheeled toy. However, if the individual has such a vehicle but does not ride it for any reason, including parent or caregiver does not think he or she is ready, mark "0."		N/O

Comments

Motor Skills Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Sitting | Walking and Running | Play Activity | Standing | Creeping and Crawling

✔ Check for Comments below

GROSS, continued

	30	Jumps or hops forward at least three times.	2 1 0	DK	
4+ →	31	Hops on one foot at least once without falling; may hold on to something for balance.	2 1 0	DK	
	32	Climbs on and off high objects (for example, jungle gym, 4-foot slide ladder, etc.).	2 1 0	DK	
	33	Walks down stairs, alternating feet; may use railing.	2 1 0	DK	
	34	Runs smoothly, with changes in speed and direction.	2 1 0	DK	
	35	Rides bicycle with training wheels for at least 10 feet.	2 1 0	DK	
		Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a bicycle. However, if the individual has a bike but does not ride it for any reason, including parent or caregiver does not think he or she is ready, mark "0."	N/O		
	36	Catches beach ball-sized ball (from at least 6 feet away) with both hands.	2 1 0	DK	
	37	Hops forward on one foot with ease.	2 1 0	DK	
	38	Skips at least 5 feet.	2 1 0	DK	
	39	Catches tennis or baseball-sized ball (from at least 10 feet away), moving to catch it if necessary.	2 1 0	DK	
	40	Rides bicycle with no training wheels without falling.	2 1 0	DK	
		Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a bicycle. However, if the individual has a bike but does not ride it for any reason, including parent or caregiver does not think he or she is ready, mark "0."	N/O		

Comments

Item Before Basal ____ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

N/O Total + ☐

Sum of 2s and 1s + ☐

**If the total of DK and/or Missing is greater than 2, do not score subdomain.*

Gross Raw Score = ☐ SUM

Manipulating Objects | Drawing and Using Scissors | Using Keyboard

FINE

<1 →	1	Reaches for toy or object.	2 1 0	DK	
	2	Picks up small objects (no larger than 2 inches on any side); may use both hands.	2 1 0	DK	
	3	Moves object from one hand to the other.	2 1 0	DK	
	4	Squeezes squeaky toy or object.	2 1 0	DK	
	5	Picks up small object with thumb and fingers.	2 1 0	DK	
1, 2 →	6	Removes object (for example, a block or clothespin) from a container.	2 1 0	DK	
	7	Puts object (for example, a block or clothespin) into container.	2 1 0	DK	
	8	Turns pages of board, cloth, or paper book, one at a time.	2 1 0	DK	
3, 4 →	9	Stacks at least four small blocks or other small objects; stack must not fall.	2 1 0	DK	
	10	Opens doors by turning doorknobs.	2 1 0	DK	
	11	Unwraps small objects (for example, gum or candy).	2 1 0	DK	

Motor Skills Domain, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Manipulating Objects | Drawing and Using Scissors | Using Keyboard

FINE, continued

				✔ Check for Comments below
	12	Completes simple puzzle of at least two pieces or shapes.	2 1 0 DK	
	13	Turns book or magazine pages one by one.	2 1 0 DK	
	14	Uses twisting hand-wrist motion (for example, winds up toy, screws/ unscrews lid of jar, etc.).	2 1 0 DK	
	15	Holds pencil in proper position (not with fist) for writing or drawing.	2 1 0 DK	
	16	Colors simple shapes; may color outside lines.	2 1 0 DK	
5 →	17	Builds three-dimensional structures (for example, a house, bridge, vehicle, etc.) with at least five small blocks.	2 1 0 DK	
	18	Opens and closes scissors with one hand.	2 1 0 DK	
	19	Glues or pastes two or more pieces together (for example, for art or science projects, etc.).	2 1 0 DK	
	20	Uses tape to hold things together (for example, torn page, art project, etc.).	2 1 0 DK	
	21	Draws more than one recognizable form (for example, person, house, tree, etc.). **Scoring Tip:** Mark a "2" if the individual draws two or more recognizable forms; mark a "1" if the individual draws one form; mark a "0" if the individual does not draw any recognizable forms.	2 1 0 DK	
	22	Makes recognizable letters or numbers.	2 1 0 DK	
	23	Draws circle freehand while looking at example.	2 1 0 DK	
	24	Uses scissors to cut across paper along a straight line.	2 1 0 DK	
	25	Colors simple shapes; colors inside the lines.	2 1 0 DK	
6+ →	26	Cuts out simple shapes (for example, circles, squares, rectangles, etc.).	2 1 0 DK	
	27	Uses eraser without tearing paper.	2 1 0 DK	
	28	Draws square freehand while looking at example.	2 1 0 DK	
	29	Draws triangle freehand while looking at example.	2 1 0 DK	
	30	Ties knot.	2 1 0 DK	
	31	Draws straight line using a ruler or straightedge.	2 1 0 DK	
	32	Unlocks dead-bolt, key, or combination locks that require twisting. **Scoring Tip:** You may mark "N/O" for No Opportunity if there are no dead-bolt, key, or combination locks in the home.	2 1 0 DK N/O	
	33	Cuts out complex shapes (for example, stars, animals, alphabet letters, etc.).	2 1 0 DK	
	34	Uses keyboard, typewriter, or touch screen to type name or short words; may look at keys. **Scoring Tip:** You may mark "N/O" for No Opportunity if there is no computer in the home.	2 1 0 DK N/O	
	35	Ties secure bow.	2 1 0 DK	
	36	Uses a keyboard to type up to 10 lines; may look at the keys. **Scoring Tip:** You may mark "N/O" for No Opportunity if there is no computer in the home.	2 1 0 DK N/O	

Comments

Item Before Basal ☐ × 2 = ☐

Basal Item Through Ceiling Item:

DK and/or Missing Total* + ☐

N/O Total + ☐

Sum of 2s and 1s + ☐

**If the total of DK and/or Missing is greater than 2, do not score subdomain.*

Fine Raw Score = ☐ SUM

Maladaptive Behavior Index

Response Options: 2 = Usually, 1 = Sometimes, 0 = Never

				✔ Check for Comments below
INTERNALIZING				
3+ →	1	Is overly dependent (that is, clings to caregiver, teacher, brother, or sister).	0 1 2	
	2	Avoids others and prefers to be alone.	0 1 2	
	3	Has eating difficulties (for example, eats too fast or too slowly, hoards food, overeats, refuses to eat, etc.).	0 1 2	
	4	Has sleep difficulties (for example, sleepwalks, has frequent nightmares, sleeps significantly more or less than typical for his or her age.	0 1 2	
	5	Refuses to go to school or work because of fear, feelings of rejection or isolation, etc.	0 1 2	
	6	Is overly anxious or nervous.	0 1 2	
	7	Cries or laughs too easily.	0 1 2	
	8	Has poor eye contact (that is, does not look at or face others when speaking or spoken to).	0 1 2	
	9	Is sad for no clear reason.	0 1 2	
	10	Avoids social interaction.	0 1 2	
	11	Lacks energy or interest in life.	0 1 2	

Comments

Sum of 2s and 1s ☐

Internalizing Raw Score = ☐

EXTERNALIZING				
3+ →	1	Is impulsive (that is, acts without thinking).	0 1 2	
	2	Has temper tantrums.	0 1 2	
	3	Intentionally disobeys and defies those in authority.	0 1 2	
	4	Taunts, teases, or bullies.	0 1 2	
	5	Is inconsiderate or insensitive to others.	0 1 2	
	6	Lies, cheats, or steals.	0 1 2	
	7	Is physically aggressive (for example, hits, kicks, bites, etc.).	0 1 2	
	8	Is stubborn or sullen.	0 1 2	
	9	Says embarrassing things or asks embarrassing questions in public (for example, "You're fat," or "What's that big red thing on your nose?").	0 1 2	
	10	Behaves inappropriately at the urging of others.	0 1 2	

Comments

Sum of 2s and 1s ☐

Externalizing Raw Score = ☐

Maladaptive Behavior Index, *continued*

Response Options: **2** = Usually, **1** = Sometimes, **0** = Never

OTHER				✔ Check for Comments below
3+ →	1	Sucks thumb or fingers.	0 1 2	
	2	Wets bed or must wear diapers at night.	0 1 2	
	3	Acts overly familiar with strangers (for example, holds hands, hugs, sits on lap, etc.).	0 1 2	
	4	Bites fingernails.	0 1 2	
	5	Has tics (that is, involuntary blinking, twitching, head shaking, etc.).	0 1 2	
	6	Grinds teeth during the day or night.	0 1 2	
	7	Has a hard time paying attention.	0 1 2	
	8	Is more active or restless than others of same age.	0 1 2	
	9	Uses school or work property (for example, telephone, Internet access, office supplies, etc.) for unapproved personal purposes.	0 1 2	
	10	Swears.	0 1 2	
	11	Runs away (that is, is missing for 24 hours or longer).	0 1 2	
	12	Is truant from school or work.	0 1 2	
	13	Ignores or doesn't pay attention to others around him or her.	0 1 2	
	14	Uses money or gifts to "buy" affection.	0 1 2	
	15	Uses alcohol or illegal drugs during the school or work day.	0 1 2	

Comments

Sum of 2s and 1s ☐

Other Raw Score = ☐

Internalizing Raw Score + ☐

Externalizing Raw Score + ☐

Other Raw Score + ☐

Maladaptive Behavior Index Raw Score* = ☐ SUM

**Sum the Internalizing, Externalizing, and Other Raw Scores to obtain the Maladaptive Behavior Index Raw Score.*

Maladaptive Behavior Critical Items

Response Options: **2** = Usually, **1** = Sometimes, **0** = Never, **S** = Severe, **M** = Moderate

CRITICAL ITEMS

				✔ Check for Comments below
3+ →	1	Engages in inappropriate sexual behavior (for example, exposes self, masturbates in public, makes improper sexual advances, etc.).	0 1 2 S M	
	2	Is obsessed with objects or activities (for example, constantly repeats words or phrases, is preoccupied with mechanical objects, etc.).	0 1 2 S M	
	3	Expresses thoughts that do not make sense (for example, talks about hearing voices, seems delusional, etc.).	0 1 2 S M	
	4	Has strange habits or ways (for example, makes repetitive noises, odd hand movements, etc.).	0 1 2 S M	
	5	Consistently prefers objects to people (for example, pays more attention to objects than to people, etc.).	0 1 2 S M	
	6	Displays behaviors that cause injury to self (for example, bangs head, hits or bites self, tears at skin, etc.).	0 1 2 S M	
	7	Destroys own or another's possessions on purpose.	0 1 2 S M	
	8	Uses bizarre speech (for example, has conversations with self in public, speaks in phrases or sentences that have no meaning, repeats same word or phrase over and over, etc.).	0 1 2 S M	
	9	Is unaware of what is happening around him or her (for example, seems to be in a "fog," stares blankly, etc.).	0 1 2 S M	
	10	Rocks back and forth repeatedly.	0 1 2 S M	
	11	Is unusually fearful of ordinary sounds, objects, or situations.	0 1 2 S M	
	12	Remembers odd information in detail years later.	0 1 2 S M	
	13	Is unable to complete a normal school or work day because of chronic pain or fatigue.	0 1 2 S M	
	14	Is unable to complete a normal school or work day because of psychological symptoms	0 1 2 S M	

The Maladaptive Behavior Critical Items section does not yield a raw or derived score. To include this section in your interpretation of Vineland–II results, transfer responses of 2 or 1 (and the severity rating, S or M) to the Vineland–II Score Summary page.

Comments

Appendix V: The Hospital Anxiety and Depression Scale

The following questions focus on how *you* feel about things. Please read each item and circle the reply underneath the item which comes closest to how you have been feeling in the past week. Do not take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response.

1. I feel tense or 'wound up'

Most of the time | A lot of the time | From time to time | Not at all

2. I still enjoy the things I used to enjoy

Very definitely and quite badly | Yes, but not too bad | A little, but it doesn't worry me | Not at all

3. I get a sort of frightened feeling as if something awful is going to happen

Definitely as much | Not quite so much | Only a little | Hardly at all

4. I can laugh and see the funny side of things

As much as I always could | Not quite so much now | Definitely not so much now | Not at all

5. Worrying thoughts go through my mind

A great deal of the time | A lot of the time | Only a little | Hardly at all

6 I feel cheerful

Not at all | Not often | Sometimes | Most of the time

7. I can sit at ease and feel relaxed

Definitely | Usually | Not often | Not at all

8. I feel as if I am slowed down

Nearly all the time | Very often | Sometimes | Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach

Not at all | Occasionally | Quite often | Very often

10. I have lost interest in my appearance

Definitely | I don't take as much care as I used to | I may not take quite as much care | I take just as much care as ever

11. I feel restless as if I have to be on the move

Very much indeed | Quite a lot | Not very much | Not at all

12. I look forward with enjoyment to things

As much as I ever did | Rather less than I used to | Definitely less than I used to | Hardly at all

13. I get sudden feelings of panic

Very often indeed | Quite often | Not very often | Not at all

14. I can enjoy a good book, radio or TV programme

Often | Sometimes | Not often | Very seldom

Appendix W: Trainee's Statement of Epistemological Position

The researcher took a positivist epistemological position during the implementation of this research project. The researcher had limited experience in the area prior to carrying out the project, with very little experience in the field of genetic syndromes but some experience with people with intellectual disability and neurodevelopmental conditions. This allowed the author to take an objective viewpoint of the findings, holding no prior conceptions or misconceptions. A positivist position takes the viewpoint that research is objective and can be carried out using measurable techniques. The researcher perceived themselves as independent of what was being collected. This stance was reflected in selecting a research method where questionnaires, which were predominately completed by participants via an online survey, produced quantitative data. Statistical analysis was then utilised to draw conclusions and interpretations.

Appendix X: Chronology of Research Process

Date	Stage of Research/Activity
October to December 2015	Research presentations by supervisors Initial meeting with research supervisor
January to March 2016	First year literature review to support development of research idea
March 2016	Visit to research centre with supervisor to meet other members of the team
March to May 2016	Development of initial research proposal
June 2016	Peer review of research proposal at University of Leicester
September 2016	Research proposal amended and refined following feedback
October 2016 to January 2017	Preparation for ethics application and the obtainment of study sponsorship
January to June 2017	Re-planning of research project following changes and delays in ethics application
June 2017 to March 2018	Participants recruitment and data collection Online survey active for participants Telephone interviews with participants
September 2017	Database search for systematic literature review
February 2018	Draft literature review submitted for review
March to April 2018	Data analysis Draft research report submitted for review
May 2018	Thesis submission
*June to July 2018	*Preparation for viva
*July to September 2018	*Dissemination of findings through poster presentation and submission for publication

*intended activities and dates

Appendix Y: Guidelines for Authors in Target Journal for Literature Review

Molecular Autism, retrieved from https://molecularautism.biomedcentral.com/submission-guidelines on 29th March 2018.

Submission guidelines

Our 3-step submission process

1. **Before you submit**

Now you've identified a journal to submit to, there are a few things you should be familiar with before you submit.

- Make sure you are submitting to the most suitable journal - Aims and scope

Aims and scope

Molecular Autism is a peer-reviewed, open access journal that publishes high-quality basic, translational and clinical research that has relevance to the etiology, pathobiology, or treatment of autism and related neurodevelopmental conditions. Research that includes integration across levels is encouraged. Molecular Autism publishes empirical studies, reviews, and brief communications.

We encourage submissions from a range of fields including (but not restricted to) genetics, molecular neurobiology, neuropathology, neuroimaging, cognitive neuroscience, epidemiology, and biomarker discovery. Molecular Autism also publishes articles on screening, diagnosis and classification, including articles that consider subgrouping to refine our understanding of basic mechanisms. Intervention studies are also welcome, especially when considered with respect to revealing causal mechanisms.

Although the primary focus is on conditions on the autism spectrum (including Asperger syndrome), the scope encompasses molecular research into related neurodevelopmental conditions such as specific language impairment, dyspraxia, and specific or general developmental delays; and into related medical syndromes such as fragile X syndrome, tuberous sclerosis, and Rett syndrome.

Molecular Autism also considers articles with no molecular data but which, in the long-term, may close the gap from molecule to behavior in autism. The journal welcomes reports and reviews of good science that proceed from either end of this complex chain of events: from molecule upwards, or from behavior downwards. Reports and reviews can be basic and/or translational.

- Understand the costs and funding options - Fees and funding

Article-processing charges

Open access publishing is not without costs. Molecular Autism therefore levies an article-processing charge of £1370.00/$2145.00/€1745.00 for each article accepted for publication.

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  - Review

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Key aims of Reviews are to provide systematic and substantial coverage of mature subjects, evaluations of progress in specified areas, and/or critical assessments of emerging technologies.

Molecular Autism does not generally consider unsolicited reviews.

  - Methodology
  - Short report
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  - Viewpoint

Click the relevant link to find style and formatting information for the article you are going to submit.

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The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

present a title that includes, if appropriate, the study design e.g.:

"A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"

or for non-clinical or non-research studies: a description of what the article reports

list the full names, institutional addresses and email addresses for all authors

if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below

indicate the corresponding author

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The Abstract should not exceed 350 words and should be structured with a background, main body of the abstract and short conclusion. Please minimize the use of abbreviations and do not cite references in the abstract.

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Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the article, its aims, a summary of a search of the existing literature and the issue under discussion.

Main text

This should contain the body of the article, and may also be broken into subsections with short, informative headings.

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This should state clearly the main conclusions and include an explanation of their relevance or importance to the field.

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Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

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Consent for publication

Availability of data and material

Competing interests

Funding

Authors' contributions

Acknowledgements

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Please see below for details on the information to be included in these sections.

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